Anesthesia and Analgesia

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

WE STRIVE ALWAYS FOR WORLD CONQUEST OF PAIN

1922

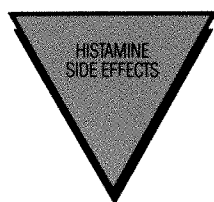## In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

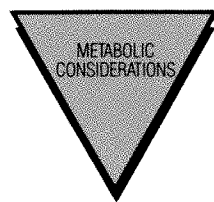## Minimizes
the variables

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

▽ NORCURON® requires no dosage adjustments to avoid histamine release

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

cuk-H02993-32-P024556

Anesthesia and Analgesia

Journal of International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122   Telephones: (216) 295-1124 or 295-1130

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1990 B.B. SANKEY
ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1990 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **January 15, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1990 Award(s) will be announced at the Annual Scientific Meeting (64th Congress) of the International Anesthesia Research Society to be held at the Sheraton–Waikiki Hotel, Honolulu, Hawaii, March 9–13, 1990.

Anesthesia and Analgesia

Contents

Editorial

Cardiovascular Control Mechanisms during Anesthesia

Jean Marty, MD and J. G. Reves, MD

Acute homeostatic control of arterial blood pressure is mediated in part by the baroreceptor reflex. Any disorders that produce change in arterial blood pressure from its set point are compensated by reflex responses which operate through alterations in heart rate, myocardial contractility, venous tone, and arterial resistance. These responses are mediated by sympathetic and vagal systems. Since autonomic reflexes are under the control of the central nervous system, it can be expected that anesthesia will alter baroreflex function, and indeed, Bristow et al. (1) showed 20 years ago that anesthesia depressed baroreflex control of heart rate in humans (1). This finding has important implications in the clinical interpretation of blood pressure and heart rate changes which are used daily by anesthesiologists to monitor surgical patients during anesthesia. The analysis of circulatory parameters to assess, for instance, the adequacy of blood replacement to compensate blood loss during surgical procedures, must take into account that homeostatic regulation of arterial blood pressure may be altered by the anesthetic drugs used. In the 1970s, Vatner and Braunwald (2) emphasized the consequences of the disruptive effect of anesthesia on sympathetic contribution to cardiovascular control mechanisms and particularly the difficulties encountered in the interpretation of experiments designed in anesthetized animals to investigate cardiac physiology or cardiac pharmacology. In addition, they showed that impairment of baroreflex

responses produced by anesthesia markedly decreased the tolerance to hemorrhage, since arterial blood pressure declined similarly in anesthetized dogs and in denervated dogs (denervation of baroreceptors) with an identical amount of hemorrhage (2). Also, recent work implies that autonomic imbalance and altered baroreflex function may be responsible for mortal arrhythmias (3,4).

An important question is the degree to which each anesthetic agent alters baroreflex function, since this could influence the clinical decision regarding choice of a particular anesthetic drug. The extent of depression of baroreflex responses has been evaluated for many anesthetic drugs in animal and man. Baroreflex control of heart rate has been most frequently studied since pressor and depressor pharmacological tests are easier to perform in humans or in intact animals than methods evaluating the other components of baroreflex function. Most inhalational anesthetic agents attenuate baroreflex control of heart rate in humans and this depressant effect is more marked with halothane and enflurane than with isoflurane (5–7). Elegant, systematic studies conducted by the Milwaukee research group directed by Kampine have established that halogenated agents have multiple sites of action (8,9) leading to depression of baroreflex function. Benzodiazepines (10) and most intravenous anesthetics except ketamine and etomidate (11) also depress or modify the baroreflex response. Therefore, alteration of baroreflex responses during general anesthesia appears to be mainly related to a nonspecific effect due to anesthesia itself rather than to specific receptor-mediated modification.

Previous anesthesia studies have been for the most part conducted before surgery began. Surgery is known to modify adrenergic activity because of the noxious stimuli (12); consequently, surgery and probably recovery from general anesthesia might alter baroreflex activity. Within the context of clinical in-

teractions of anesthesia and surgery, the question of the evolution of baroreflex changes during and after operation arises. Takeshima and Dohi (13) in this issue provide some interesting answers to this poorly explored area. These investigators have examined modifications of baroreflex control of heart rate during an entire course of clinical anesthesia in patients receiving either isoflurane or enflurane. They found a similar depression of baroreflex function with both agents. This effect remained unchanged during surgery. Normal baroreflex functions quickly returned during the recovery phase in isoflurane patients.

The work presented is not without problems. The comparison of the two drugs is limited by the design of the study. First, it is not clear if anesthesia was randomly allocated. Second, to compare the actions of isoflurane and enflurane properly, it is essential to evaluate them at equipotent concentrations. However, the end-tidal concentrations of isoflurane and enflurane used in this study indicate that equi-effective (equi-MAC) concentrations were not achieved in the two groups. Third, baseline heart rate was higher in isoflurane patients than in enflurane patients complicating the comparison. In addition, in both groups, control heart rate was perhaps influenced by atropine. This may have been responsible, at least in part, for the low baroreflex sensitivity observed during the control period. Finally, to properly determine the relative speed of return of baroreflex responses during recovery of anesthesia, a similar depth of anesthesia would have been desirable in the two groups.

The comparison between enflurane and isoflurane is not the most important information in this work. The two interesting points raised by this study are: 1) the absence of modifications of baroreflex sensitivity during surgery, even if anesthesia was deepened; and 2) the rapid recovery of baroreflex response in the postoperative period. This gives us new knowledge about multiple determinations of baroreflex function in clinical situations. Carter et al. (14) have also demonstrated that restoration of baroreflex control of heart rate occurred quickly at the end of anesthesia, but the present investigation spans the entire operative period. The clinical implications of the new results are important if one considers that a depressed baroreflex response implies a limited ability to compensate for hemodynamic pertubations such as hypovolemia or hemorrhage. However, this and previous studies do not answer the important clinical question: what happens to the other components of baroreflex responses? Takeshima and Dohi evaluated only heart rate responses to pressor and depressor stimuli, whereas the role of vasomotor

tone of arterial and venous circulation appears more crucial to the maintenance of blood pressure than heart rate responses. In addition, the evolution of cardiopulmonary baroreflex control of peripheral resistance is an important factor in the regulation of arterial blood pressure and should be investigated with all anesthetics since it has been reported that halothane attenuates it (15). To get a complete answer regarding baroreflex function investigations in addition to the heart rate response can be performed since Goldstein et al. (16) demonstrated that the different aspects of baroreflex responses can be completely evaluated by specific techniques evaluating the multiple components. Nevertheless, because the correlations between each component of baroreflex responses are good (16), we might assume that all components of the baroreflex are simultaneously altered, even if the magnitude of these modifications may be somewhat different.

Finally, although the data of this study do not address the question, it should be asked whether an anesthetic agent or technique that decreases baroreflex responses is deleterious or not. The answer is probably yes at the time of induction of anesthesia, when circulatory alterations that require integrity of baroreflex to maintain arterial blood pressure homeostasis occur (17), such as acute hypovolemia or direct anesthetic depression. At this time, an anesthetic agent that does not alter baroreflex function would be preferable. During maintenance of anesthesia, a depression of baroreflex function implies that blood loss will produce a decrease in arterial blood pressure. This phenomenon may facilitate the diagnosis of hemodynamic changes. By contrast, if baroreflex functions are preserved, hidden blood loss will be compensated until the limit of homeostatic mechanisms are reached: then decompensation may suddenly occur. A previous report comparing mortality resulting from acute hypovolemia in animals anesthetized with either thiopental, which attenuates baroreflex, or with ketamine which does not, did not demonstrate a difference between the two groups (18), suggesting that alteration of baroreflex may not affect survival. The influence of patient disease, e.g., diabetes (19,20), is another possible contributing factor to baroreflex dysfunction during anesthesia, and the question of interaction of anesthesia with diabetes needs to be answered. The relevance of baroreflex studies would be strengthened if these questions were examined.

In summary, the study of Takeshima and Dohi provides interesting new information regarding the evolution of baroreflex function during anesthesia and surgery. Importantly, this work stimulates new

questions regarding the clinical implications of alterations in baroreflex function for the management of anesthetized patients with hemorrhage, hypovolemia, or certain disease states.

References

1. Bristow JD, Prys-Roberts C, Fischer A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. Anesthesiology 1969;31:422-8.

2. Vatner SF, Braunwald E. Cardiovascular control mechanisms in the conscious state. N Engl J Med 1975;293:970-4.

3. Swartz PJ, Emilio V, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death: new insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation 1988;78:969-79.

4. Rea RF, Marins JB, Mark AL. Baroreflex impairment and sudden death after myocardial infarction. Circulation 1988; 78:1072-4.

5. Duke PC, Fownes D, Wade JG. Halothane depresses baroreflex control of heart rate in man. Anesthesiology 1977;46:184-7.

6. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during isoflurane and enflurane nitrous oxide anesthesia. Anesthesiology 1980;52:221-3.

7. Kotrly KJ, Ebert TJ, Vucins SE, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173-9.

8. Seagard JZ, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP. Halothane and the carotid sinus reflex: evidence for multiple sites of action. Anesthesiology 1982;57:191-202.

9. Seagard JZ, Hopp FA, Bosnjak ZJ, Elegbe EO, Kampine JP. Extent and mechanisms of halothane sensitization of the carotid sinus baroreceptors. Anesthesiology 1983;58:432-7.

10. Marty J, Gauzit R, Lefevre P, Couderc E, Farinotti R, Henzel D, Desmonts JM. Effects of diazepam and midazolam on barore-

flex control of heart rate and on sympathetic activity in humans. Anesth Anal 1986;65:113-9.

11. Bernards C, Marrone B, Priano L. Effect of anesthetic induction agents on baroreceptor function (abstract). Anesthesiology 1985;63:A31.

12. Halter JB, Pflug AE, Porte D. Mechanisms of plasma catecholamines increase during surgical stress in man. J Clin Endoc Metab 1977;45:936-40.

13. Takeshima R, Dohi S. Comparison of arterial baroreflex function in humans anesthetized with enflurane and isoflurane. Anesth Analg 1989;69:284-90.

14. Carter JA, Clarke TNS, Prys-Roberts C, Spelina KR. Restoration of baroreflex control of heart rate during recovery from anesthesia. Br J Anaesth 1986;58:415-21.

15. Ebert TJ, Kotrly KJ, Vucins EJ, Pattison CZ, Kampine JP. Halothane anesthesia attenuates cardiopulmonary baroreflex control of peripheral resistance in humans. Anesthesiology 1985;63:668-74.

16. Golstein DS, Horwitz D, Keiser HR. Comparison of techniques for measuring baroreflex sensitivity in man. Circulation 1982; 66:432-9.

17. Reves JG, Gelman S. Cardiovascular effects of intravenous anesthetic drugs. In: Covino, Fozzard, Rehder, Strichartz, eds. Effects of anesthesia. American Physiological Society (Clinical Physiology Series) 1985:179-93.

18. Weiskopt RD, Bogetz MS, Roizen MF, Reid IA. Cardiovascular and metabolic sequelae of inducing anesthesia with ketamine or thiopental in hypovolemic swine. Anesthesiology 1981; 60:214-9.

19. Olshan AR, OConnor DT, Cohen IM, Mitas JA, Stone RA. Baroreflex dysfunction in patients with adult-onset diabetes and hypertension. Am J Med 1983;74:233-42.

20. Eckberg DL, Harkins SW, Fritsch JM, Musgrave GE, Gardner DE. Baroreflex control of plasma norepinephrine and heart period in healthy subjects and diabetic patients. J Clin Invest 1986;78:366-74.

Myocardial and Cerebral Drug Concentrations and the Mechanisms of Death after Fatal Intravenous Doses of Lidocaine, Bupivacaine, and Ropivacaine in the Sheep

Craig Nancarrow, FFARACS, PhD, Albert J. Rutten, BSc, William B. Runciman, FFARACS, PhD, Laurence E. Mather, PhD, FFARACS, Ronda J. Carapetis, Dip Lab Med, Colin F. McLean, and Scott F. Hipkins, MSc

NANCARROW C, RUTTEN AJ, RUNCIMAN WB, MATHER LE, CARAPETIS RJ, McLEAN CF, HIPKINS SF. Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine, and ropivacaine in the sheep. Anesth Analg 1989;69:276–83.

This paper reports the cardiovascular effects of intentionally toxic intravenous doses of lidocaine, bupivacaine, and ropivacaine and the mechanisms of death. Fatal doses of lidocaine, bupivacaine, and ropivacaine were established in sheep treated with successive daily dose increments of each drug. The mean fatal dose of lidocaine ($\pm$ SD) was 1450 ± 191 mg (30.8 ± 5.8 mg/kg), that of bupivacaine was 156 ± 31 mg (3.7 ± 1.1 mg/kg), and that of ropivacaine was 325 ± 108 mg (7.3 ± 1.0 mg/kg); thus the ratio of fatal doses was approximately 9:1:2. In four out of four lidocaine-treated animals, respiratory depression with bradycardia and hypotension without arrhythmias were the causes of death. Three out of four bupivacaine-treated animals died after the sudden onset of ventricular tachycardia/fibrillation without hypoxia or acidosis; the fourth died in a similar manner to the lidocaine-treated animals. Three out of five animals given ropivacaine died in a manner resembling the fatal effects of lidocaine-treated animals, but unlike the lidocaine-treated animals, in all three sheep there were also periods of ventricular arrhythmias. The remaining two ropivacaine-treated sheep died as a result of the sudden onset of ventricular tachycardia/fibrillation. The mean percentages of the fatal dose found in the myocardium was 2.8 ± 0.7 for lidocaine-treated animals, 3.3 ± 0.9 for bupivacaine-treated animals, and 2.2 ± 1.4 for ropivacaine-treated animals; the corresponding percentages in whole brain were, respectively, 0.71 ± 0.01, 0.71 ± 0.21, and 0.89 ± 0.27.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine, ropivacaine. TOXICITY—lidocaine, bupivacaine, ropivacaine.

In a previous report from this laboratory (1), the central nervous and cardiovascular system effects of single intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine were examined in conscious adult sheep. Within the putative equi-anesthetic equivalent-to-clinical dose range studied in these experiments, there were no appreciable differences between the drugs with nonfatal doses. Similar conclusions have been reached by others studying only lidocaine and bupivacaine using different experimental designs and different species (2).

Other studies performed in animals (2), which were initiated by reports of clinical problems with bupivacaine (3), indicate that there is a greater chance of a fatal outcome after bupivacaine than from lidocaine administration. Ropivacaine is currently undergoing investigation (4) before possible clinical use. The aim of this study was to examine the cardiovascular effects of intentionally toxic and lethal doses of these agents. This was done to determine the fatal dose and mechanisms of death for each agent, and to determine whether possible disproportionality between fatal doses and anesthetic potencies was due to differences in the distribution of the agents into the

heart and the brain or to intrinsic pharmacological differences between them.

Methods

Experimental Design

Approval was given by the institutional ethics review committee for the study to be performed. Sheep were prepared with chronic intravascular cannulae for cardiovascular monitoring and serial blood sampling. In each experiment, the animal was supported in a sling designed to enable unimpeded cardiovascular measurements and prevent the animal from injury during local anesthetic-induced convulsions. Animals received either lidocaine, bupivacaine, or ropivacaine by intravenous infusion over 3 min; if the animal survived, the dose of the agent was increased the next day until a fatal outcome resulted.

Animal Preparation

Thirteen sheep underwent vascular cannulations using methods and materials previously described (1,5). A brief description is given here.

After surgical exposure of the blood vessels in the neck, three arterial cannulae were placed via the carotid artery with their tips positioned approximately 2 cm above the aortic valve. One cannula was for collection of arterial blood samples, one for measurement of mean arterial blood pressure (MAP), and the other was a special purpose catheter that acted as an introducer for the passage into the left ventricle via the aortic valve of a high-fidelity catheter tipped pressure transducer (PC350, Millar Instruments, Houston, TX). Venous cannulae were placed both in the posterior vena cava (PVC) for the infusion of the local anesthetics and in the right atrium for bolus injection of cold dextrose during cardiac output measurements in conjunction with a flow-directed thermodilution catheter (Edwards Laboratories Inc., Santa Ana, CA) placed in the pulmonary artery.

To detect cardiac dysrhythmias, a quadrapolar intracardiac electrocardiograph (ECG) wire (USCI Ltd., Billerica, MA) was inserted via a small puncture in the right internal jugular vein with its tip positioned in either the right atrium or the coronary sinus. That the animals were in good health with normal cardiovascular homeostatic mechanisms after such procedures had been verified previously (5). The animals were allowed to recover from the cannulation procedures for at least 3 days.

Cardiovascular and Hemodynamic Monitoring

The protocol for the recording of hemodynamic and electrocardiographic events has been described previously (1).

Arterial blood samples were obtained for the determination of blood gas tensions and acid-base status before drug administration and at regular intervals after drug administration.

Drug Doses

Four sheep (mean weight 47.8 ± 5.7 kg) were given lidocaine, four (mean weight 43.6 ± 4.2 kg) were given bupivacaine and five sheep (mean weight 45.1 ± 6.4 kg) were given ropivacaine. The drugs were diluted with water to a volume of 30–40 mL and infused over 3 min using a constant-rate infusion pump. Stock solutions before dilution were lidocaine HCl 10% and bupivacaine HCl 0.5% (Astra Pharmaceuticals Pty., Ltd., Sydney, Australia). Ropivacaine HCl stock solutions were prepared from the powder form as a 2% solution in water. Doses and concentrations (Table 1) are expressed in terms of the local anesthetic salt.

Whole-Blood Drug Concentrations

Arterial blood samples (0.2–1 mL) were obtained for drug assay at approximately 30-sec intervals for 5 min after the start of drug infusion and at 1-min intervals for a further 5 min. Drug concentrations in whole blood were determined by gas chromatography with nitrogen selective detection after solvent extraction (6). To examine the continuous relationship between drug effects and arterial blood concentration of drugs, the concentrations at the times of onset of convulsions were interpolated from arterial blood drug concentration–time graphs.

Tissue Collection and Determination of Tissue Drug Content

After a fatal infusion, the heart and brain were removed within 25 min in order to determine organ drug distribution. The heart was removed by transection through the great vessels approximately 2 cm above the level of the aortic valve, and 2 cm below the caudal border of the right atrium. Blood was immediately expressed from the cardiac chambers, as much as possible of the nonmuscle tissue was re-

Table 1. Details of the Experiments Used to Determine Fatal Doses of Lidocaine, Bupivacaine, and Ropivacaine

Sheep no.	Weight (kg)	Dose (mg over 3 min)	Maximum measured arterial drug concentration (mg/L)	Time at which maximum arterial concentration measured (min)	Arterial drug concentration at start of convulsion (mg/L)	Time of start of convulsion (min)	Convulsive dose (mg)
Lidocaine-treated animals							
1	52	400	28	2.7	28	2.3	307
		600	38	1.5	35	1.3	260
		800	57	2.0	46	1.0	267
		1000	80	3.0	33	0.8	267
		1200	96	1.5	50	0.8	320
		1400	94	1.0	70	0.8	373
		1600[a] (4)	244	6.0	45	0.8	427
2	41	600	49	1.5	38	1.2	240
		1000	95	3.0	30	0.8	267
		1200	97	2.7	72	0.8	320
		1400[a] (5)	140	3.0	51	0.8	373
3	45	600	62	3.0	51	1.5	300
		1000	68	1.1	67	1.1	367
		1200	104	2.0	100	1.1	440
		1400	125	3.2	79	1.0	467
		1600[a] (4.5)	174	3.1	63	0.9	480
4	53	600	59	1.4	50	1.2	240
		1000	104	2.9	50	1.0	333
		1200[a] (6)	220	4.1	70	0.5	200
Bupivacaine-treated animals							
5	39	50	5.7	2.5	5.3	2.0	33
		75	7.6	2.7	6.4	1.8	45
		100	8.3	1.9	4.9	1.8	60
		125	15.4	2.7	9.6	1.0	42
		150	20.0	3.0	11.1	1.0	50
		175	NA	—	NA	1.0	58
		200[a] (4.5)	29.5	3.1	17.6	1.0	67
6	44	100	10.0	3.1	5.1	1.9	64
		125	13.9	2.6	11.0	2.2	92
		150[a] (3)	19.8	4.6	13.0	1.7	85
7	42.5	100	11.9	2.5	4.1	1.8	60
		125	13.5	2.0	12.7	1.8	75
		150[a] (4)	14.1	1.9	12.6	1.5	75
8	49	100	12.5	2.5	12.5	2.5	83
		125 (6.5)	16.2	1.9	15.4	1.8	75
Ropivacaine-treated animals							
9	43	100	9.2	3.0	8.8	2.7	90
		125	11.0	3.0	9.8	2.2	92
		150	14.8	3.0	11.9	2.1	105
		175	17.2	3.0	13.8	2.0	117
		200	17.9	2.0	14.8	1.7	113
		225	19.6	3.0	16.0	1.7	128
		250	23.7	3.1	20.0	2.0	167
		275	25.3	3.0	17.7	1.5	183
		300	24.9	3.0	20.2	1.8	180
		325[a] (5.5)	28.9	3.0	20.5	1.7	184
10	55.5	150	10.1	2.2	9.7	2.1	105
		175	10.6	2.5	10.4	2.7	158
		200	11.8	2.5	11.7	2.2	150
		250[a] (3.5)	15.8	1.9	14.1	1.5	125
11	44	150	18.7	3.0	18.7	3.0	150
		225	29.5	3.0	25.2	2.5	188
		225[a] (4.7)	24.9	3.0	21.3	2.3	173

Table 1. (continued)

Sheep no.	Weight (kg)	Dose (mg over 3 min)	Maximum measured arterial drug concentration (mg/L)	Time at which maximum arterial concentration measured (min)	Arterial drug concentration at start of convulsion (mg/L)	Time of start of convulsion (min)	Convulsive dose (mg)
12	38	175	7.2	2.0	6.9	2.2	128
		200	13.8	2.0	13.1	1.7	113
		225	16.0	2.0	14.7	1.6	120
		250	16.8	2.0	15.3	2.3	192
		275	17.2	2.0	16.7	1.7	162
		300	19.0	2.0	18.2	1.4	140
		325[a] (6.5)	22.4	2.0	22.4	2.0	217
13	45	175	16.6	3.0	14.9	2.3	134
		200	17.2	3.0	17.2	3.0	200
		250	19.2	3.0	16.7	1.5	125
		275	24.5	3.0	18.0	2.2	202
		300	25.0	3.0	21.0	1.9	190
		350	30.7	3.0	27.6	1.7	198
		400	34.3	3.0	30.8	1.7	227
		500[a] (4.0)	47.3	4.0	30.0	1.3	217

[a]Denotes fatal experiment with time of death (min) in parentheses.

moved, and the weight was recorded. The myocardial samples were then stored frozen (−20°C) until analyzed for drug concentrations. The brain was removed by transection at the level of the lower border of the pons, weighed, and stored frozen as for the heart tissue.

In one sheep treated with each drug, serial biopsies of the left ventricular and atrial surfaces were taken starting at 12–15 min after death until 30 min after death with the heart still *in situ*. These separate samples were analyzed for tissue drug concentrations to determine whether drug metabolism or continued tissue drug distribution occurred between the death of the animal and removal of the heart.

Myocardium or brain was chopped with a scalpel and then mixed in a stainless steel cannister with a weight of 2 M HCl equal to twice that of the tissue and was then homogenized for 10 min (Omni Mixer, Sorvall Inc., Newtown, CT). Duplicate aliquots (200 μL) of homogenate were used for each assay. Apart' from the initial preparation in acid, the remaining analytical procedures (solvent extraction, gas chromatography) were the same as those described for blood samples (6). A standard curve was prepared by the addition of known amounts of lidocaine, ropivacaine, and bupivacaine to similarly prepared homogenates of heart and brain tissue obtained from animals not previously exposed to these drugs. The mean tissue drug concentration was calculated from the average of the duplicated samples.

Statistical Analysis

Pairwise comparisons on the ratio of the mean fatal doses were performed by Student's *t*-test.

Comparisons of the percentages of the doses found in heart and brain were performed using one-way analysis of variance.

Results

Sixty-six experiments were performed on 13 animals (Table 1).

Central Nervous System Effects

Convulsions occurred with all doses used. The doses (±SD) infused to the times of onset of convulsions were 320 ± 65 mg (6.8 ± 0.8 mg/kg), 69 ± 12 mg (1.6 ± 0.2 mg/kg), and 155 ± 40 mg (3.5 ± 0.5 mg/kg) for lidocaine, bupivacaine, and ropivacaine respectively (Table 1). Therefore, the ratio of the mean convulsant doses (lidocaine/bupivacaine/ropivacaine) was approximately 5:1:2. The mean arterial lidocaine, bupivacaine, and ropivacaine concentrations at the onset of convulsions were in a similar ratio, 54 ± 19, 10.1 ± 4.3, and 17.1 ± 5.9 mg/L, respectively (Table 1).
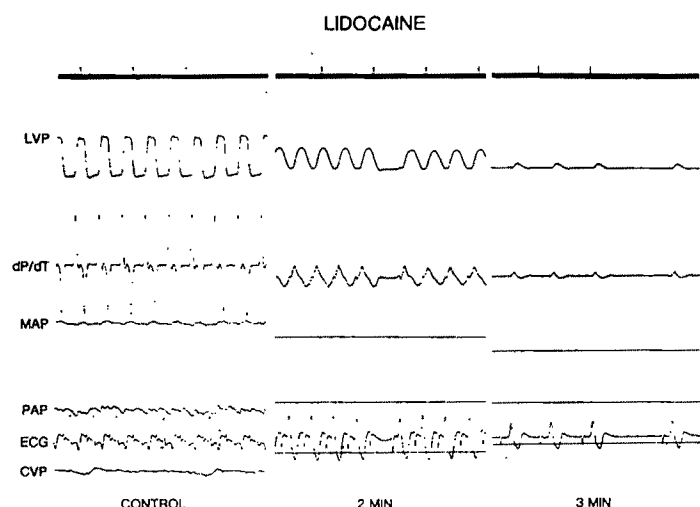
LIDOCAINE

Figure 1. Hemodynamic and electrocardiographic changes during the fatal intravenous infusion over 3 min of 1600 mg of lidocaine HCl to sheep 1.

Cardiovascular Effects, Mechanisms of Death and Their Relations to Arterial Blood Drug Concentrations

The mean of the fatal doses was 1450 ± 191 mg (30.8 ± 5.8 mg/kg) in lidocaine-treated animals, 156 ± 31 mg (3.6 ± 1.1 mg/kg) for bupivacaine-treated animals, and 325 ± 108 mg (7.3 ± 1.0 mg/kg) for ropivacaine-treated animals (Table 1). The ratio of the mean fatal doses (lidocaine/bupivacaine/ropivacaine) was thus 9:1:2. When the fatal doses of bupivacaine were compared to those of lidocaine divided by 4 (in order to compensate for the lower local anesthetic potency of lidocaine), there was a statistically significant difference between the drug treatment groups ($P < 0.005$). For there to be just no significant difference between the groups ($P = 0.05$), the hypothetical local anesthetic potency ratio (bupivacaine/lidocaine) would have to be 5.6:1. When the fatal doses of bupivacaine were compared to those of ropivacaine divided by 1.5 (to compensate for the lower local anesthetic potency of ropivacaine), there was no significant difference ($P = 0.16$) between the drug treatment groups. The ratios of mean fatal doses to the mean convulsive doses were 4.5:1 for lidocaine, 2.2:1 for bupivacaine, and 2.1:1 for ropivacaine.

In animals given lidocaine (sheep 1–4), death was produced by a marked reduction in myocardial contractility together with bradycardia, hypotension, and respiratory depression. Electrocardiographic changes in all lidocaine-induced deaths included configurations consistent with first degree atrioventricular block and increased width of the ventricular complex consistent with intraventricular conduction block. Serial chart recordings from one animal, which is typical of the others, are presented in Figure 1.

Table 2. Mean Arterial Po$_2$ (mm Hg) during Fatal Experiments

Lidocaine treated		
Sheep 1, 2, 3, 4	Control	95
	2 min	85
	4 min	68
Bupivacaine treated		
Sheep 5	Control	85
	2 min	109
	4 min	24
Sheep 6, 7, 8	Control	98
	2 min	120
Ropivacaine treated		
Sheep 10, 12, 13	Control	100
	2 min	87
	3 min	61
	5 min	39
Sheep 9, 11	Control	100
	2 min	114
	3 min	97
	5 min	103

In animals given bupivacaine, the mechanism of death in three of the four animals (sheep 6–8) was the sudden onset of ventricular tachycardia and resultant ventricular fibrillation without antecedent hypoxia (Table 2). Serial chart recordings from one animal, which is typical of the other two animals which died in ventricular fibrillation, are presented in Figure 2. For the remaining animal (sheep 5), death was produced by progressive respiratory depression with hypoxia (Table 2), bradycardia, and hypotension after a dose of 200 mg and thus resembled the fatal effects of lidocaine.

In animals given ropivacaine, the mechanism of death in three of the five animals (sheep 10, 12, 13) resembled the fatal effects of lidocaine, i.e., progressive bradycardia, hypotension with hypoxia. How-

BUPIVACAINE

Figure 2. Hemodynamic and electrocardiographic changes during the fatal intravenous infusion over 3 min of 150 mg of bupivacaine HCl to sheep 6.
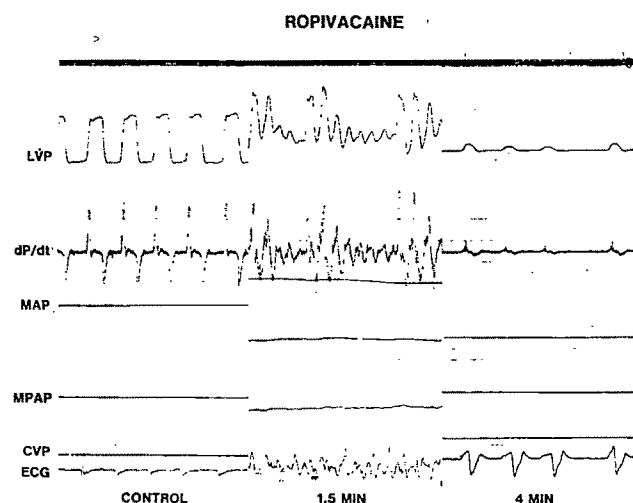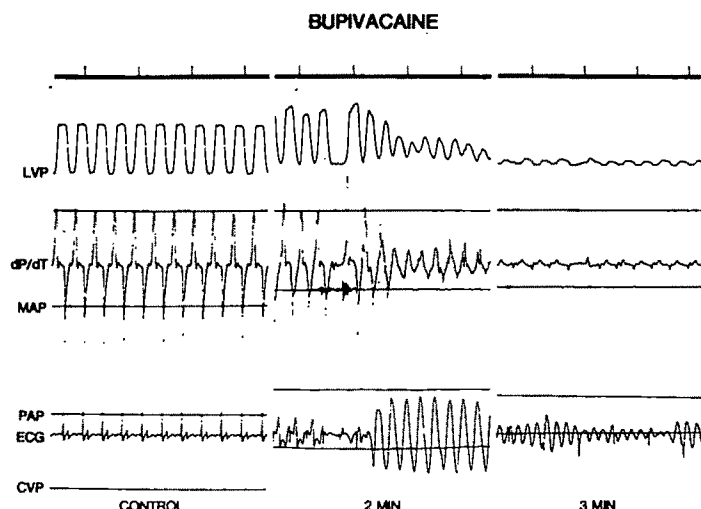
ROPIVACAINE

Figure 3. Hemodynamic and electrocardiographic changes during the fatal intravenous infusion over 3 min of 500 mg of ropivacaine HCl to sheep 13.

ever, unlike the lidocaine-treated animals, in all three sheep there were periods of ventricular arrhythmias before the final lidocaine-like progressive cardiovascular deterioration (Figure 3). The other two animals (sheep 9, 11) died after the sudden onset of ventricular arrhythmias without antecedent hypoxia.

Distribution of Lidocaine and Bupivacaine into Heart and Brain

The mean percentage of the lidocaine dose found in the heart was 2.8 ± 0.7; that for bupivacaine was 3.3 ± 0.9 and that for ropivacaine was 2.2 ± 1.4. These values were not significantly different ($P = 0.35$). The mean percentage of drug dose found in the brain was 0.71 ± 0.009 for lidocaine-treated animals, 0.71 ± 0.21

Table 3. Concentrations of Lidocaine, Bupivacaine, and Ropivacaine in Myocardial Samples Obtained at Different Times after Death

	Time sample obtained after death (min)	Tissue drug concentration (μg/g)
Lidocaine	15	133
	19	122
	26	120
	29	121
Bupivacaine	12	16.1
	19	13.0
	28	13.6
	33	15.1
Ropivacaine	15	25.8
	20	22.5
	25	22.9
	30	23.6

for bupivacaine-treated animals, and 0.89 ± 0.27 for ropivacaine-treated animals. These values were not significantly different ($P = 0.35$).

Results of the serial tissue samples obtained postmortem from a lidocaine-, a bupivacaine-, and a ropivacaine-treated animal (Table 3) showed that there was no systematic loss of drug after death.

Discussion

The design used in this investigation to study local anesthetic-induced toxicity *in vivo* was different from that used by others. In the latter, either single or repeated intravenous bolus injections or prolonged intravenous infusions were used in conscious or anesthetized and/or open-chested animals of a variety of species (1,2). Each preparation and study design had different pharmacodynamic and pharma-

cokinetic implications and simulated the clinical problem of inadvertent intravascular local anesthetic injection to different extents. For this study, we decided upon a compromise policy. Short (3-min) intravenous infusions were administered to conscious animals, which would allow observation of effects during the onset of toxicity but which would still reasonably represent the clinical situation of accidental intravenous injection. It was considered important to compare not only the fatal doses but also the tissue distribution of lidocaine, bupivacaine and ropivacaine in relation to the fatal doses. Tissue distribution has been determined in several other investigations but the results are not strictly comparable with the present study because of differences in methodology. For various reasons, each of these studies have severe limitations; e.g., the use of [^{3}H]bupivacaine without determination of the contribution of ^{3}H-labeled bupivacaine metabolites to the measured drug concentrations (7), the use of tissue/blood drug concentration ratios without verification of steady state conditions (8), and the use of absolute tissue concentrations rather than the fractions of dose as a basis to compare drugs (9).

The relationship between drug toxic effects and the rapidly changing blood drug concentrations after bolus injections (or brief infusions) is more difficult to discern than when blood concentrations are changing more slowly after neural blockade or after intravenous infusions used to assess toxicity. Where such data have been obtained in humans, it appears that arterial blood bupivacaine concentrations in excess of 4 mg/L have been involved (10). However, it is also possible to find other reports of equally high concentrations without toxic sequelae (11); the circumstances of "toxic" blood drug concentrations need to be reported with great care. After rapid intravascular injection or rapid absorption after perineural injection, drug concentrations in both blood and tissues are initially changing rapidly due to the state of disequilibrium, but with slower absorption after perineural injection a closer relationship between blood and tissue concentrations would be expected so that "toxic" blood concentrations reported under these circumstances would be more meaningful.

Although bupivacaine is approximately four times more potent than lidocaine as a local anesthetic, it is approximately nine times more lethal. The factor by which the lidocaine fatal doses were divided to produce just no significant difference ($P = 0.05$) when compared with fatal doses of bupivacaine was 5.6. From this result, it may be calculated that the same volumes of 0.36% bupivacaine and 2% lidocaine would have the same potential to produce a fatal

outcome under the conditions of this study. In clinical practice, 2% lidocaine is considered to have equal local anesthetic effects to 0.5-0.75% bupivacaine. Therefore, the margin of safety would be smaller after the inadvertent intravascular administration of bupivacaine than after the inadvertent injection of an equi-anesthetic dose of lidocaine. This difference, however, is not due to a greater uptake into the brain or myocardium of the bupivacaine dose injected. The lack of difference between fatal doses of bupivacaine compared to ropivacaine (divided by 1.5) initially suggests there is little difference in the toxic potential of these two agents. However, the values used for the local anesthetic potency of ropivacaine are derived from initial estimates in laboratory animals only (4). Further interpretation of the results of the present study requires comparisons of the clinical local anesthetic potency and block duration of ropivacaine with those of lidocaine and bupivacaine.

There were marked differences in the mechanism of death after either lidocaine or bupivacaine: this is consistent with work reported by others (2,12-15). Bupivacaine may be arrhythmogenic in the absence of marked hypoxia, respiratory or metabolic acidosis, hyperkalemia, or hypotension. Such arrhythmias have been reported to consist of either supraventricular tachycardias, atrioventricular conduction blocks, ventricular tachycardias, multiform premature ventricular contractions or wide QRS complexes. Recent electrophysiological experiments have provided insights into the mechanism by which bupivacaine might induce cardiac arrhythmias. It is now apparent that both lidocaine and bupivacaine can exert their cardiac electrophysiological effects by binding to the same specific receptor sites in cardiac sodium channels. However, there are significant differences in the duration of effects for each drug: bupivacaine has a longer duration of effect than lidocaine on cardiac electrophysiology (16,17). The magnitude of the effect, and therefore the ratio of potencies, however, depends on local conditions; hyperkalemia or acidosis increases the propensity for bupivacaine to induce conduction block and inexcitability at relatively lower concentrations than lidocaine (18,19). The effect of acidosis, however, is not mediated through a greater myocardial (or brain) uptake of the agent (6).

The results of the present study suggest that ropivacaine may have cardiac electrophysiological effects intermediate to those of lidocaine and bupivacaine. Even in ropivacaine-treated animals which eventually died a "lidocaine-like" death there were ventricular arrhythmias earlier in the experiments. The mechanisms of production of these cardiac electrophysiological effects will require further studies

similar to those already performed for bupivacaine (16,17).

In summary, when the results reported in this paper are considered along with other recent findings, there is substantial evidence that the greater cardiotoxicity of bupivacaine compared to lidocaine is due to cardiac arrhythmia formation. An important finding of this study is that cardiac arrhythmias also occurred after ropivacaine but were not necessarily the final mechanism of death. The percentages of the administered dose found in the heart and brain after lethal dosage were similar for all three agents. These results, therefore, support the proposition that the observed differences in cardiotoxicity between the agents are due to qualitative differences with respect to their effects on cardiac electrophysiology, and not because of disproportionate uptakes into the myocardium. The results also suggest that further investigation of ropivacaine is indicated to more accurately determine its clinical local anesthetic potency and toxicity.

References

1. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine and ropivacaine in the sheep. Anesth Analg 1989;69:291–9.

2. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736–46.

3. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.

4. Åkerman B, Hellberg IB, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 1988;32:571–8.

5. Runciman WB, Ilsley AH, Mather LE, Carapetis R, Rao MM. A sheep preparation for studying interactions between blood flow and drug disposition. I. Physiological profile. Br J Anaesth 1984;56:1015–28.

6. Nancarrow C, Mather LE, Runciman WB, Upton RN, Plummer JL. The influence of acidosis on lidocaine and bupivacaine distribution into myocardium and brain of the sheep. Anesth Analg 1987;66:925–35.

7. Sjöstrand U, Widman B. Distribution of bupivacaine in the rabbit under normal and acidotic conditions. Acta Anaesthesiol Scand 1973;suppl 50.

8. Halpern SH, Eisler EA, Shnider SM, Shapiro DA, Levinson G, Rosen MA, Johnson J, Jones MJ. Myocardial tissue uptake of bupivacaine and lidocaine after intravenous injection in normal and acidotic rabbits (abstract). Anesthesiology 1984;61:A208.

9. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur GR, Covino BG. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63:134–9.

10. Moore DC, Balfour RI, Fitzgibbon D. Convulsive arterial plasma levels of bupivacaine and response to diazepam therapy. Anesthesiology 1979;50:454–6.

11. Tucker GT, Mather LE. Physicochemical properties, absorption and disposition of local anesthetics: pharmacokinetics. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: JB Lippincott, 1988.

12. Sage DJ, Feldman HS, Arthur GR, Doucette AM, Norway SB, Covino BG. The cardiovascular effects of convulsant doses of lidocaine and bupivacaine in the conscious dog. Reg Anaesth 1985;10:175–83.

13. Kasten GW, Martin ST. Comparison of resuscitation of sheep and dogs after bupivacaine-induced cardiovascular collapse. Anesth Analg 1986;65:1029–32.

14. Kasten GW. Amide local anesthetic alterations of effective refractory period temporal dispersion: relationship to ventricular arrhythmias. Anesthesiology 1986;65:61–6.

15. Nath S, Haggmark S, Johansson G, Reiz S. Different depressant and electrophysiologic cardiotoxicity of local anesthetics: an experimental study with special reference to lidocaine and bupivacaine. Anesth Analg 1986;65:1263–70.

16. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985;62:396–405.

17. Moller RA, Covino BG. Cardiac electrophysiologic effects of lidocaine and bupivacaine. Anesth Analg 1988;67:107–14.

18. Rosen MA, Thigpen JW, Kotelko DM, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–96.

19. Bosnajk ZJ, Stowe DF, Kampine JP. Comparison of lidocaine and bupivacaine depression of sinoatrial nodel activity during hypoxia and acidosis in adult and neonatal guinea pigs. Anesth Analg 1986;65:911–7.

Comparison of Arterial Baroreflex Function in Humans Anesthetized with Enflurane or Isoflurane

Reiko Takeshima, MD and Shuji Dohi, MD

TAKESHIMA R, DOHI S. Comparison of arterial baroreflex function in humans anesthetized with enflurane or isoflurane. Anesth Analg 1989;69:284-90.

To compare the depressive effects of isoflurane and enflurane on the arterial baroreflex function, we examined baroreflex control of heart rate during the entire course of clinical anesthesia. Isoflurane and enflurane were found to have similar depressive effects on the baroreflex control of heart rate when used in combination with N_2O and O_2. Suppression in the baroreflex sensitivity, defined by the slopes of regression line (change in msec of RR interval per mm Hg increase or decrease in systolic blood pressure) was from 7.1 ± 3.9 to 1.8 ± 0.7 msec/mm Hg in patients given isoflurane and from 7.8 ± 4.3 to 3.0 ± 1.9 msec/mm Hg in those given enflurane when evaluated by a pressor test (bolus IV phenylephrine). The slope of the depressor test (bolus IV nitroglycerin) also decreased from 4.7 ± 2.8 to 1.9 ± 1.5 msec/mm Hg with isoflurane and from 5.6 ± 3.2 to 2.3 ± 1.2 msec/mm Hg with enflurane. During surgery in which anesthetic concentration invariably needed to be increased, the suppression of the baroreflex sensitivity remained unchanged in both groups of patients. During recovery, the arterial baroreflex function in patients given isoflurane recovered more rapidly than that in patients given enflurane. This difference may be related to a more minor degree of suppression of isoflurane on the autonomic nervous system compared to enflurane.

Key Words: ANESTHETICS, VOLATILE—enflurane, isoflurane. BLOOD PRESSURE, REFLEX CONTROL. RECEPTORS, PRESSORECEPTORS. REFLEXES, BARORECEPTORS.

Anesthesia is known to attenuate the arterial baroreflex function, an important neural control system for maintaining cardiovascular stability in humans (1–11). Among presently used volatile anesthetics, isoflurane has been suggested by Kotrly et al. (7) and Seagard et al. (12) as depressing baroreflex regulation of heart rate less than either enflurane or halothane in both humans and animals. These authors attribute tachycardia during isoflurane anesthesia to this greater preservation of the baroreflex function. Isoflurane may provide sympathetic activation with a reflex response to the accompanying arterial hypotension because there may be less suppression of the autonomic nervous system. This possible beneficial effect of isoflurane anesthesia has remained to be verified (13), and there are no comparative studies in this regard. Further, the only available data concern-

ing the baroreflex function of inhalational anesthetics are those tested before surgery in young, nonpremedicated, adult patients aged between 18 and 35 years (4,5,7).

It is well known both that the baroreflex function progressively decreases with advancing age (14,15) and, further, that noxious stimuli may modify baroreceptor-induced circulatory responses during anesthesia (16). Isoflurane anesthesia without surgical intervention appears to be less cardiac-depressant than either enflurane or halothane in a closed chest dog preparation (17), but the anesthetic effects on the responsiveness of the autonomic nervous system may differ not only among agents, but also during ongoing surgical stimulation. Therefore, in the present study, we compared the arterial baroreflex control of heart rate between isoflurane and enflurane anesthesia in patients aged between 42 and 72 years during an entire course of clinical anesthesia, i.e., before induction of anesthesia, after induction of anesthesia, during surgery, and after recovery from anesthesia.

Materials and Methods

Patient Selection and Study Groups

Twenty-four ASA physical status I patients, 42–72 years of age, without any history of cardiopulmonary or neurological disorders, were subjects in the present study. The study protocol was approved by the Jutaku Kenkyu Committee of the University of Tsukuba Hospital and our local review committee, and informed consent was obtained from each patient. All patients received hydroxyzine, 50 mg, and atropine, 0.5 mg IM (as suggested by the committee) for premedication 60 min before the arrival in operating room where they were divided into two groups. Group 1 received isoflurane (12 patients) and group 2 received enflurane (12 patients) in addition to 67% N_2O and oxygen.

Study Procedures

An electrocardiograph (ECG) monitor (lead II or V), a peripheral IV catheter, an arterial (radial) blood pressure (AP) catheter, and a beat-to-beat basic heart rate (HR) monitor (tachometer) were placed in each patient while in the supine position. The ECG, HR, and AP were continuously recorded on a polygraph. Each patient was then asked twice to make three forceful coughs within 5 sec on command to assess overall autonomic activity (10,15). Pressor (P) and depressor (D) tests were then performed (10): P, the bolus injection of phenylephrine, 62.5–125 μg, IV; D, the bolus injection of nitroglycerin, 125–250 μg, IV; these doses were chosen to elevate or depress arterial blood pressure by 20–30 mm Hg (10) according to patient's age. A period of stabilization between the tests allowed AP and HR to return to the pretest level.

All patients were then anesthetized with thiamylal, 4–5 mg/kg, IV, and O_2 and isoflurane or enflurane. Tracheal intubation was facilitated with succinylcholine chloride, 1 mg/kg. All patients were mechanically ventilated (a tidal volume of 10–12 mL/kg at a respiratory rate of 10–12 breaths/min) with 67% nitrous oxide and oxygen with isoflurane or enflurane. End-tidal concentrations of CO_2 and isoflurane or enflurane (Normac, Datex) were continuously measured in each patient. Constancy of ventilation and oxygenation also was ensured before each set of the tests by measurements of arterial blood gas tensions while awake and anesthetized.

The second pressor and depressor tests were performed 15–20 min after the start of isoflurane or enflurane inhalation and repeated 30–45 min after surgical procedures was begun (the third tests). During these periods, inspired concentrations of the anesthetics were changed because of decreases or increases in AP during surgery, but the concentrations were kept constant for at least 15 min before and during the third tests. After completion of surgery the patient's trachea was extubated and the last pressor and depressor tests were performed 10–15 min after removal of tracheal tube. Before the last tests were performed we confirmed that all patients were able to breathe adequately with spontaneous respiration and supplemented oxygen, responded to verbal commands, and had stable levels of AP and HR.

Pressor and depressor tests' data were analyzed using least-squares linear regression analysis on the linear region (above threshold) of the sigmoid relation between systolic AP and HR interval (7). The slope of regression line expressed as msec/mm Hg was defined as the baroreflex sensitivity. Only the individual regression slopes with correlation coefficients >0.80 were included in the group mean.

Arterial blood samples were collected for measurements of arterial blood gas tensions, and plasma concentrations of potassium, sodium, glucose, and insulin (the double-antibody method) before each set of the tests, because anesthetics and surgical stress could induce hyperglycemia and impaired release of insulin, which may affect baroreceptor reflexes and normal function of the cardiovascular system. During surgery, all patients received intravenous lactated Ringer's solution; no IV glucose was given.

Paired and unpaired Student's t-tests were used to analyze the results. We used a value of $P < 0.05$ to indicate statistical significance. All values were expressed as mean ± 1 SD.

Results

Comparison of the awake baseline data in the isoflurane and enflurane groups showed no statistically significant difference in age, height, weight, HR response to cough, duration of surgery and anesthesia, surgical blood loss and fluid replacement (Table 1) and awake values of AP and HR. Arterial blood pressure decreased significantly during anesthesia and surgery, but increased significantly and similarly after recovery from anesthesia in the two groups. Changes in AP after either phenylephrine or nitroglycerin were similar in the two groups throughout the study (Table 2), but changes in HR associated with changes in AP differed significantly in the four stages of the measurements.

Pressor and depressor slopes were similar before induction of anesthesia in two groups (Table 2). Both
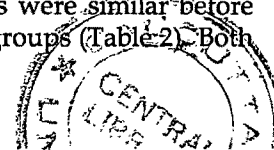
<u>Table 1</u>. Demographic Data (mean ± sd) in the Two Groups of Patients

	Age (yr)	Height (cm)	Body weight (kg)	HR response to cough (beats/min)	Duration of surgery (min)	Duration of anesthesia (min)	Blood loss (mL)	Fluid replacement (mL)
Isoflurane (N = 12)	48 ± 7	156 ± 9	57 ± 9	+12 ± 4	175 ± 71	240 ± 98	632 ± 503	2333 ± 885
Enflurane (N = 12)	52 ± 12	154 ± 12	54 ± 14	+18 ± 8	180 ± 61	250 ± 79	358 ± 307	1965 ± 501

the pressor and depressor slopes were significantly depressed with both isoflurane– or enflurane–N_2O–O_2 anesthesia, the end-tidal concentrations of which were 0.8 ± 0.2% (0.4–0.95) and 0.7 ± 0.3% (0.4–0.95), respectively. There was no significant difference in the reduction of the slopes between the two groups (71% decrease for isoflurane vs 68% decrease for enflurane; $P > 0.05$). In the presence of surgical stimulation (end-tidal concentrations of isoflurane 1.0 ± 0.3%, of enflurane 1.1 ± 0.4%) the slopes were depressed similarly with both anesthetics (Figure 1). The mean slopes of both pressor and depressor tests during recovery, which were determined when end-tidal concentration of isoflurane and enflurane were below 0.2%, were not statistically significantly different from awake control values in the isoflurane group, but those in the enflurane group were still depressed ($P < 0.05$, Figure 1). All but four of the values of correlation coefficient (R) between systolic AP and R–R intervals obtained were >0.90.

Plasma glucose concentrations increased above baseline levels equally in both groups during surgical stimulation and during recovery from anesthesia ($P < 0.05$, Figure 2). Increases in plasma glucose levels during surgery were associated with significant decreases in plasma insulin levels and continued to be elevated during emergence from anesthesia. In the isoflurane group insulin concentrations returned to baseline levels after recovery from anesthesia, whereas in the enflurane group they remained decreased (Figure 2). Arterial blood gas tensions and plasma concentrations of Na^+ and K^+ did not change significantly during the entire course of anesthesia in either group (Table 3). Pao_2 increased after induction of anesthesia because of high inspired concentration of O_2 and $Paco_2$ also showed statistically significant changes, but there was no significant difference between isoflurane and enflurane groups (Table 3).

Discussion

As previously reported in unpremedicated humans (5,7), the present results indicate that both isoflurane

and enflurane depress the arterial baroreceptor reflexes in premedicated humans when used in combination with nitrous oxide and oxygen. Although in the present study the end-tidal concentrations of isoflurane and enflurane were not identical, since 67% N_2O should decrease similarly the anesthetic requirements of both enflurane and isoflurane (in the presence of 70% N_2O, end-tidal concentrations of isoflurane and enflurane for 1 MAC anesthesia are 0.50 and 0.57, respectively [18]) and since hemodynamic variables were similar during anesthesia in both groups, we believe that anesthetic levels were comparable in the two groups. Differences in the depression of baroreceptor reflexes previously reported (25 to 5 msec/mm Hg with 0.56% enflurane, 70% N_2O, and O_2 [5]; 27.8 to 20.7 msec/mm Hg with 1 MAC isoflurane [7]) and the greater depression of the sensitivity slopes observed in the present study (7.8 to 3.0 msec/mm Hg for enflurane, 7.1 to 1.8 msec/mm Hg for isoflurane) may be related to premedication with atropine and hydroxyzine or anesthetic concentrations but mainly represent differences in ages of the patients we studied. In previous reports, only young adult patients (18–30 years of age for isoflurane [4] or 20–35 years of age for enflurane [7]) were studied, whereas in the present investigation, we studied patients above age 42 (42–72 years of age). This could also be responsible for the fact that baseline slopes of both the pressor and depressor tests in patients in the present study were less than those observed in previous reports (4,5,7,8,10) and thus perhaps could explain the greater depression of baroreflex function in the present study. We used the HR response to cough to assess cardiac autonomic integrity (15) in individual patients. The responses while awake did not significantly differ in the patients given isoflurane and those given enflurane; this suggests that the patients of both groups were comparable as far as preanesthetic autonomic activities are concerned.

Available data both in humans (1–11) and animals (12,19–26) describe anesthetic effects on the baroreflex function only in the absence of surgery. The stimulation of surgery usually increases AP and HR above levels seen after induction of anesthesia, espe-

Table 2. Hemodynamic Responses (Arterial Pressure and Heart Rate) to Phenylephrine and Nitroglycerin and Baroreflex Sensitivity (Slope) While Awake, After Induction of Anesthesia, During Surgery, and During Recovery

	Awake Pretest AP	HR	Pressor test AP	Slope	Depressor test AP	Slope	Anesthesia Pretest AP	HR	Pressor test AP	Slope	Depressor test AP	Slope	Surgery Pretest AP	HR	Pressor test AP	Slope	Depressor test AP	Slope	Recovery Pretest AP	HR	Pressor test AP	Slope	Depressor test AP	Slope
Isoflurane (Mean)	122	80	+23	7.08	-28	4.69	103[a]	88	+22	1.76[a]	-29	1.92[a]	114[a]	88	+23	2.25[a]	-25	2.20	142[a]	85	+21	4.75	-28	2.79
(±SD)	13	18	10	3.81	10	2.81	10	12	7	0.66	11	1.45	12	15	7	1.54	6	1.05	24	8	8	4.45	8	2.41
Enflurane (Mean)	129	74	+19	7.75	-22	5.56	109[a]	81	+22	2.99[a]	-25	2.28[a]	112[a]	79	+20	2.37[a]	-27	2.39[a]	146[a]	81	+21	3.52[a]	-28	1.87[a]
(±SD)	18	8	4	4.27	5	3.17	11	13	5	1.92	5	1.21	13	12	7	2.16	10	1.34	22	9	5	4.35	15	2.18

Data given as arterial pressure (mm Hg), heart rate (beats/min), and slope (msec/mm Hg). Abbreviations: AP, arterial pressure; HR, heart rate. [a]P < 0.05 vs each Awake value.
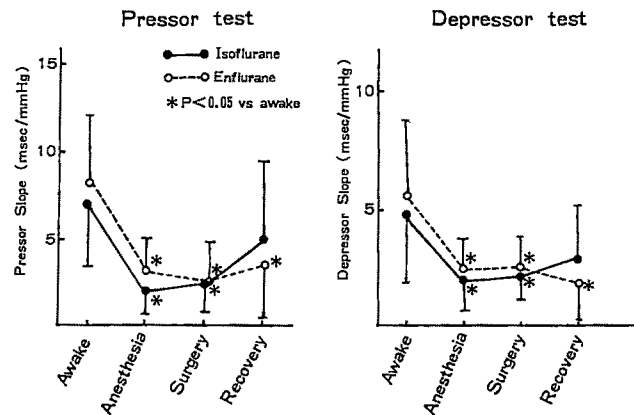
Figure 1. Pressor (phenylephrine) and depressor (nitroglycerin) tests of baroreflex activity before and after induction of anesthesia, during surgery, and during recovery in patients given isoflurane or enflurane.
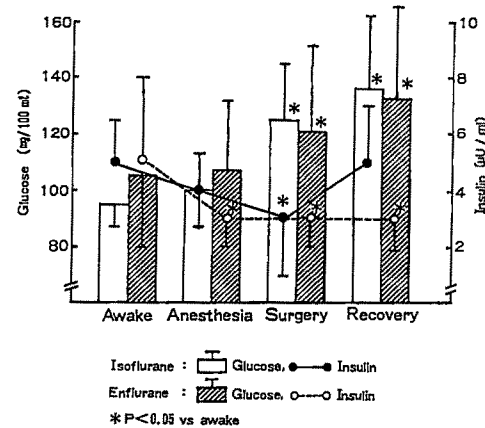
Figure 2. Plasma glucose and insulin concentrations.

cially with light levels of anesthesia. This is probably due to surgical stimulation producing increases in sympathetic nervous activity, renin–angiotensin activity, and circulating levels of catecholamines and vasopressin (11,25,27–29). For example, while isoflurane appears to directly depress vagal and sympathetic nervous activity in dose-related fashion (26), the direct depression associated with 1.5% isoflurane is compensated for by reflex increases in sympathetic tone due to the hypotension accompanying the anesthesia (30). This compensation may be attributable to better preservation of the baroreflex function during isoflurane anesthesia. We do not know of any study of enflurane similar to the present study. Noxious stimulation (16) as well as naloxone, which produces "cortical arousal" during anesthesia (31), have been found to modify or to reverse anesthetically depressed baroreceptor reflexes in experimental animals (16). In the present study, however, we failed to find that the stimulation of ongoing surgery reverses the depression of baroreflex slopes associated with

Table 3. Arterial Blood Gas Tensions and Plasma Electrolyte Levels Before and After Induction of Anesthesia, During Surgery, and During Recovery

	Awake						Anesthesia						Surgery						Recovery					
	PaO$_2$ (mm Hg)	PaCO$_2$ (mm Hg)	pH	BE (mEq/L)	Na (mEq/L)	K	PaO$_2$ (mm Hg)	PaCO$_2$ (mm Hg)	pH	BE (mEq/L)	Na (mEq/L)	K	PaO$_2$ (mm Hg)	PaCO$_2$ (mm Hg)	pH	BE (mEq/L)	Na (mEq/L)	K	PaO$_2$ (mm Hg)	PaCO$_2$ (mm Hg)	pH	BE (mEq/L)	Na (mEq/L)	K
Isoflurane (Mean)	84	42	7.41	2	140	3.71	155[a]	38[a]	7.43	2	141	3.67	149[a]	33[a]	7.46	1	140	3.51	197[a]	41	7.37	−1	140	3.50
(±SD)	7	4	0.01	2	5	0.40	28	6	0.05	3	3	0.29	26	5	0.07	3	3	0.34	68	3	0.03	2	4	0.41
Enflurane (Mean)	80	42	7.39	1	143	3.74	147[a]	37[a]	7.42	1	141	3.62	145[a]	38[a]	7.42	0	140	3.66	184[a]	43	7.36	−1	142	3.53
(±SD)	7	4	0.03	2	3	0.26	30	6	0.06	2	3	0.36	19	5	0.04	2	3	0.47	60	6	0.04	2	3	0.45

[a] $p < 0.05$ vs each Awake value.

either isoflurane or enflurane anesthesia. The initiation of surgery elicited an increase in AP and HR which per se might affect the baroreflex slopes, and we thus increased inhaled concentrations of either agent. Consequently, AP and HR before the tests did not differ significantly from AP and HR levels during anesthesia and during surgery (Table 2). In the case of anesthesia without noxious stimulation changes in basal AP and HR before pressor and depressor tests would be unlikely to modify the depression of the reflex response (5,8). Increasing inhaled concentrations of isoflurane, however, cause further depression of the baroreflex control of HR assessed by the pressor test (7). Thus, it may be inappropriate to compare the baroreflex sensitivity during anesthesia with and without surgical stimulation. Since there depressor tests before and during surgery in the present study, we believe that the surgical stimulation is likely to reverse, at least in part, the depressed baroreflex function, or to protect it from further depression, especially during isoflurane anesthesia.

In patients anesthetized with isoflurane, N$_2$O, and O$_2$, the baroreflex control of HR evaluated with the pressor and the depressor tests recovered significantly more rapidly than it did in patients given enflurane. Patients in the two groups were observed to be similarly awake and responsive at the time the tests were performed with end-tidal concentrations of isoflurane and enflurane <0.2%. We, therefore, believe that the anesthetic action rather than anesthetic levels plays an important role on the present results. It should be emphasized, however, that evaluation of the baroreflex function during the recovery periods from anesthesia was difficult because of the technical difficulties inherent in obtaining stable recordings of AP and HR (probably due to postoperative pain). We tried to carry out our studies when patients seemed to fall asleep or when they closed their eyes and had stable levels of AP and HR. Although sleep (31,32), increase in Paco$_2$ (33), and probably postoperative pain affect the baroreflex activity, the difference in responses to pressor and depressor tests during recovery between isoflurane and enflurane does not seem to be attributable to those factors. The results of a recent study indicate that the return of consciousness in the majority of young adult patients is associated with recovery of baroreflex sensitivity (assessed by the pressor test) at the end of anesthesia with either halothane or methohexital (34).

Although we believe that the difference in the baroreflex slopes between isoflurane and enflurane during recovery seems to be due to anesthetic effects on the arterial baroreflex arc including the baroreceptors, the central nervous system, ganglion transmis-

sion, and the heart, the reason(s) for this difference remain speculative. Donchin et al. (35) in studies of the effects of isoflurane–N_2O anesthesia on the central nervous system found that during the recovery periods vagal tone increases and approaches the conscious level. Because the arterial baroreflex function is maintained mainly by parasympathetic activity (36,37), this may explain the more rapid recovery of the reflex function that we observed after isoflurane. On the other hand, since depression of sympathetic activity with enflurane is concentration related and seems to recover within 25 min after its discontinuation (25), one may assume that parasympathetic activity might still be depressed by enflurane at the time when we performed our tests. In addition, though baroreflex function is associated with changes in plasma levels of Na^+ (38,39), K^+ (39), and glucose (40), plasma levels of these compounds were similar in the two groups in the present study. We found significant increases in glucose concentrations, as also observed in a previous study (41). However, as Figure 2 indicates, plasma insulin levels during recovery were still depressed in patients given enflurane, which, in the concentration range used clinically, has been reported to inhibit pancreatic islet insulin release (42). Insulin secretion is inhibited by stimulation of the sympathetic supply to the pancreas (43) and potentiated by stimulation of the parasympathetic supply to it (44), and it has been suggested that insulin is of importance for the normal function of the cardiovascular system (45). Therefore the persistent depression of baroreflex function by enflurane, even during recovery, may be attributable, at least in part, to the lack of increase in plasma levels of endogenous insulin. In addition, in the presence of blood loss due to surgery, one may consider additional, perhaps more important and different effects of isoflurane and enflurane not only on cardiopulmonary (low pressure) reflex responses, reported to be blunted by halothane anesthesia (46), but also on the renin-angiotensin system and vasopressin (47). These remain to be investigated.

In summary, isoflurane and enflurane had similar depressant effects on the baroreflex control of heart rate when used in combination with N_2O and O_2. The stimulation of ongoing surgery reverses the depressed reflex function of both agents, especially during isoflurane anesthesia. During recovery, the arterial baroreflex function in patients given isoflurane recovers more rapidly than that in patients given enflurane. The longer depression of baroreflex activity associated with enflurane might be related to its greater effect on the autonomic nervous system and, perhaps, to decreased release of insulin. We believe that the early recovery of arterial baroreflex function during isoflurane anesthesia is beneficial in view of the associated cardiovascular stability during and after anesthesia.

References

1. Bristow JD, Prys-Roberts C, Fisher A, Pickering TG, Sleight P. Effects of anesthesia on baroreflex control of heart rate in man. Anesthesiology 1969;31:422-8.

2. Mittler G, Wade J. The effect of methoxyflurane on baroreflex control of heart rate in man. Can Anaesth Soc J 1972;19:60-5.

3. Duke PC, Fownes D, Wade JG. Halothane depresses baroreflex control of heart rate in man. Anesthesiology 1977;46:184-7.

4. Duke PC, Trosky S. The effect of halothane with nitrous oxide on baroreflex control of heart rate in man. Can Anaesth Soc J 1980;27:531-4.

5. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during enflurane smf enflurane—nitrous oxide anesthesia. Anesthesiology 1980;52:221-3.

6. Chen RYZ, Matteo RS, Fan FC, Schuessler GB, Chien S. Resetting of baroreflex sensitivity after induced hypotension. Anesthesiology 1982;56:29-35.

7. Kotrly KJ, Ebert TJ, Vucins EJ, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in human. Anesthesiology 1984;60:173-9.

8. Kotrly KJ, Ebert TJ, Vucins EJ, Roering DL, Kampine JP. Baroreceptor reflex control of heart rate during morphine sulfate, diazepam, N_2O/O_2 anesthesia in humans. Anesthesiology 1984;61:558-63.

9. Dohi S, Tsuchida H, Mayumi T. Baroreflex control of heart rate during cardiac sympathectomy by epidural anesthesia in lightly anesthetized humans. Anesth Analg 1983;62:815-20.

10. Takeshima R, Dohi S. Circulatory responses to baroreflexes, Valsalva maneuver, coughing, swallowing, and nasal stimulation during acute cardiac sympathectomy by epidural blockade in awake humans. Anesthesiology 1985;63:500-8.

11. Baron JF, Decaux-Jacolet A, Edouard A, Berdeaux A, Samii K. Influence of venous return on baroreflex control of heart rate during lumbar epidural anesthesia in humans. Anesthesiology 1986;64:188-93.

12. Seagard JL, Elegbe EO, Hopp FA, Bosnjak ZJ, von Colditz JH, Kalbfleisch JH, Kampine JP. Effects of isoflurane on the baroreceptor reflex. Anesthesiology 1983;59:511-20.

13. Roy RC. Does isoflurane really preserve baroreflex responsiveness better than halothane or enflurane? Anesthesiology 1984;61:482-3.

14. Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971;29:424-31.

15. Wei JY, Rowe JW, Kestenbaum AD, Ben-Haim S. Post-cough heart rate response: influence of age, sex, and basal blood pressure. Am J Physiol 1983;245:R18-24.

16. Biber B, Martner J, Werner O. Modification by baroreceptor feedback of circulatory responses to noxious stimuli during anaesthesia in cats. Acta Anaesthesiol Scand 1983;27:391-5.

17. Merin RG. Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? Anesthesiology 1981;55:398-408.

18. Eger EI II. Isoflurane: a review. Anesthesiology 1981;55:559–76.

19. Cox RH, Bagshaw RJ. Influence of anesthesia on the response to carotid hypotension in dogs. Am J Physiol 1979;237:H424–32.

20. Ngai SH, Bolme P. Effects of anesthetics on circulatory regulatory mechanisms in the dog. J Pharmacol Exp Ther 1966;153:495–504.

21. Skovsted P, Price ML, Price HL. The effects of halothane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 1969;31:507–14.

22. Wilkinson PL, Stowe DF, Glantz SA, Tyberg JV. Heart-rate systemic blood pressure relationship in dogs during halothane anaesthesia. Acta Anaesthesiol Scand 1980;24:181–6.

23. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP. Halothane and the carotid sinus reflex: evidence for multiple sites of action. Anesthesiology 1982;57:191–202.

24. Skovsted P, Price HL. The effects of methoxyflurane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 1969;31:515–21.

25. Skovsted P, Price HL. The effects of ethrane on arterial pressure preganglionic sympathetic activity, and barostatic reflexes. Anesthesiology 1972;36:257–62.

26. Skovsted P, Sapthavichaikul S. The effects of isoflurane on arterial pressure, pulse rate, autonomic nervous activity, and barostatic reflexes. Can Anaesth Soc J 1977;24:304–14.

27. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision-MAC BAR. Anesthesiology 1981;54:390–8.

28. Kissin I, Morgan PL. Heart rate response to nociceptive stimulation as an index of anesthetic potency for enflurane. Anesthesiology 1983;58:109–10.

29. Cullen DJ, Eger EI II, Stevens WC, Smith NT, Cromwell TH, Cullen BF, Gregory GA, Bahlman SH, Dolan WM, Stoelting RK, Fourcade HE. Clinical signs of anesthesia. Anesthesiology 1972;36:21–36.

30. Seagard JL, Hopp FA, Bosnjak ZJ, Osborn JL, Kampine JP. Sympathetic efferent nerve activity in conscious and isoflurane-anesthetized dogs. Anesthesiology 1984;61:266–70.

31. Freye E, Hartung E, Schenk GK. Naloxone reverses the hypnotic effect and the depressed baroreceptor reflex of halothane anaesthesia in the dog. Can Anaesth Soc J 1983;30:235–41.

32. Conway J, Boon N, Jones JV, Sleight P. Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. Hypertension 1983;5:746–8.

33. Bristow JD, Brown EB, Cunningham DJC, Groode RC, Howson MG, Sleight P. The effects of hypercapnia, hypoxia and ventilation on the baroreflex regulation of the pulse interval. J Physiol 1971;216:281–302.

34. Carter JA, Clarke TNS, Prys-Roberts C, Spelina KR. Restoration of baroreflex control of heart rate during recovery from anaesthesia. Br J Anaesth 1986;58:415–21.

35. Donchin Y, Feld JM, Porges SW. Respiratory sinus arrhythmia during recovery from isoflurane-nitrous oxide anesthesia. Anesth Analg 1985;64:811–5.

36. Levy MN. Cardiac sympathetic-parasympathetic interactions. Fed Proc 1985;43:2598–602.

37. Eckberg DL. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. Am J Physiol 1980;239:H581–93.

38. Ferrario CM, Tramposch A, Kawano Y, Brosnihan KB. Sodium balance and the reflex regulation of baroreceptor function. Circulation 1987;75 (suppl I):I 141–48.

39. Andresen MC, Kuraoka S, Brown AM. Individual and combined actions of calcium, sodium, and potassium ions on baroreceptors in the rat. Circ Res 1979;45:757–63.

40. Appenzellar O, Goss JE. Glucose and baroreceptor function. Arch Neurol 1970;23:137–46.

41. Stevens WC, Eger ET, Joas TA, Cromwell TH, White A, Dolan WM. Comparative toxicity of isoflurane. halothane, fluroxene and diethyl ether in human volunteers. Can Anaesth Soc J 1973;20:357–68.

42. Ewart RB, Rusy BF, Bradford MW. Effects of enflurane on release of insulin by pancreatic islets in vitro. Anesth Analg 1981;60:878–84.

43. Porte D Jr, Girardier L, Seydoux J, Kanazawa Y, Posternak J. Neural regulation of insulin secretion in the dog. J Clin Invest 1973;52:210–14.

44. Bergman RN, Miller RE. Direct enhancement of insulin secretion by vagal stimulation of the isolated pancreas. Am J Physiol 1973;225:481–6.

45. Christensen NJ, Hilsted J, Hegedüs L, Madsbad S. Effects of surgical stress and insulin on cardiovascular function and norepinephrine kinetics. Am J Physiol 1984;247:E29–34.

46. Ebert TJ, Kotrly KJ, Vucins EJ, Pattison CZ, Kampine JP. Halothane anesthesia attenuates cardiopulmonary baroreflex control of peripheral resistance in humans. Anesthesiology 1985;63:668–74.

47. Share L. Vascular volume and blood level of antidiuretic hormone. Am J Physiol 1962;202:791–4.

Hemodynamic and Central Nervous System Effects of Intravenous Bolus Doses of Lidocaine, Bupivacaine, and Ropivacaine in Sheep

Albert J. Rutten, BSc, Craig Nancarrow, FFARACS, PhD, Laurence E. Mather, PhD, FFARACS, Anthony H. Ilsley, PhD, William B. Runciman, FFARACS, PhD, and Richard N. Upton, BSc

RUTTEN AJ, NANCARROW C, MATHER LE, ILSLEY AH, RUNCIMAN WB, UPTON RN. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Anesth Analg 1989;69:291–9.

Lidocaine hydrochloride (HCl) (80–320 mg), bupivacaine HCl (20–80 mg), and ropivacaine HCl (30–120 mg) were administered as intravenous bolus doses to conscious sheep (n = 18; average body weight 45 kg) that had previously placed intravascular cannulae for hemodynamic monitoring and for obtaining blood samples. The mean convulsive doses and arterial blood concentrations were ~110 mg and 40 mg/L, respectively, for lidocaine HCl, 45 mg and 14 mg/L for bupivacaine HCl, and 60 mg and 20 mg/L for ropiv-

acaine HCl. After subconvulsive doses of each agent, there were minimal cardiovascular effects. After convulsive doses, there were marked increases in heart rate, mean arterial pressure, pulmonary artery pressure, cardiac output, systemic vascular resistance, left ventricular end diastolic pressure, and myocardial contractility. Ventricular fibrillation caused death in two sheep after bupivacaine (80 mg) and in two sheep after ropivacaine (90 and 120 mg) administration. With sublethal doses, the hemodynamic responses to these agents were qualitatively and quantitatively similar when compared with their local anesthetic potencies.

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine, ropivacaine. TOXICITY—local anesthetic.

Studies of acute toxicity in laboratory animals have shown bupivacaine to be approximately four times more potent than lidocaine (1,2) and this value has become generally accepted as the basis for probable toxic doses of these agents in humans (2,3). Based on the relative dosage intervals, the relative rates of absorption and blood concentrations after nerve blocking procedures, and the relative degrees of binding in plasma (4), the expected clinical safety of bupivacaine has generally been considered to be not worse than that of lidocaine when doses are scaled for equal effect—despite the greater activity and intrinsic toxicity of bupivacaine (5). Moreover, it has also been generally accepted that, although the central nervous (CNS) and the cardiovascular systems

are both subject to local anesthetic-induced toxicity, the latter is more resistant because cardiovascular toxicity occurs at blood local anesthetic concentrations approximately two to four times greater than those at which central nervous toxicity occurs (6,7).

After these views were questioned (8), a variety of investigations performed in vivo and in vitro confirmed that the longer-acting amide-type local anesthetic agents do have a greater probability of causing potentially fatal cardiotoxicity than their shorter-acting counterparts. The evidence involved has been reviewed recently (9) from which it is clear that both pharmacodynamic and pharmacokinetic factors must be considered when accounting for the differences between the agents.

Ropivacaine hydrochloride (HCl) monohydrate (Astra Lakemedel AB, Sweden), a recently developed long-acting amide local anesthetic agent currently undergoing investigation prior to possible clinical use, is an enantiomerically pure structural homologue of bupivacaine. Preliminary studies of its local anesthetic activity in different species indicate that ropivacaine is an effective local anesthetic agent with potency similar to that of bupivacaine (10). Ropiv-

acaine is longer acting than bupivacaine upon infiltration, equally effective in peripheral (sciatic) nerve block, and slightly shorter acting in subarachnoid and epidural anesthesia (10). In the latter two tests, 0.75% and 1.0% ropivacaine had activity similar to that of 0.5% and 0.75% bupivacaine, respectively.

The aim of this study was to determine the central nervous and cardiovascular system effects of intravenously administered bolus doses of lidocaine, bupivacaine, and ropivacaine in a conscious sheep preparation. The dose range studied was chosen to simulate the inadvertant intravascular administration of these agents as used in clinical practice in humans.

Methods

Approval was given by the institutional ethics review committee for these studies to be performed. Multiple studies were performed in each of 18 conscious sheep with intravascular catheters previously placed to allow hemodynamic monitoring and the sampling of blood for biochemical and drug analyses; the preparation and its physiological profile have been described in detail elsewhere (11). The animals were selected from a breeding stock of 1–2-year-old Merino ewes with hemoglobin type A (12) and a narrow range of body weights (mean 45.5 kg, sD = 5.9).

Animal Preparation

The general methods and materials used for animal preparation have been described in detail by Runciman et al. (11); the methods specifically developed for these studies are described here. During general anesthesia and after surgical exposure of the blood vessels in the neck, three arterial catheters were placed via the right carotid artery with their tips positioned ~2 cm above the aortic valve. One was for collection of arterial blood samples, another was for measurement of mean arterial blood pressure, and the third was a special purpose catheter which acted as an introducer for the passage into the left ventricle of a pressure transducer tipped cathleter (PC350, Millar Instruments, Inc., Houston, TX). Venous catheters were placed via the right jugular vein, one with its tip in the posterior vena cava (PVC) for the injection of drugs, and two others in the right atrium for the injection of cold dextrose during cardiac output (CO) determinations and for central venous pressure (CVP) measurements. Cardiac output was determined using a flow directed thermodilution catheter (Edwards Laboratories, Inc., Santa Ana, CA)

in the pulmonary artery. A quadrapolar intracardiac electrocardiograph (ECG) wire (USCI Ltd., Billerica, MA) was inserted with its tip in either the right atrium or the coronary sinus to detect possible arrhythmias. The animals were allowed to recover from the surgical procedures for a period of at least 3 days. That the animals remained in good health with normal cardiovascular homeostatic mechanisms after preparation had been confirmed previously (11).

Placebo Experiments

"Placebo" experiments were performed to determine the influence of laboratory activity on responses of the animals. An intravenous bolus of saline (0.9%, 5 mL) was administered into each of two animals and the monitoring procedures described below were carried out.

Local Anesthetic Experiments

Bolus doses of 2% lidocaine HCl (80, 150, 200, or 320 mg), 0.5% bupivacaine HCl (20, 37.5, 50, or 80 mg), or 2% ropivacaine HCl (30, 45, 60. 90. or 120 mg) were rapidly administered (<5 sec) into the PVC catheter; the ratio of the doses for lidocaine and bupivacaine (4:1) corresponded to the commonly accepted ratio of their local anesthetic potencies (1 4). The ratio between the lowest and highest doses of ropivacaine and those of bupivacaine (3:2) was based upon published data on their potency ratio and durations of action for neural blockade (10). The intermediate doses were used to estimate the doses of the agents at which 50% of the animals were likely to convulse (CD_{50}). Only one dose was administered to any animal on any day; at least 18 hr was allowed between successive doses for the animals to recover and for clearance of the drugs. Previously published studies (13) and ongoing studies from the authors' laboratory have shown that the "elimination" half-life of these agents in the sheep is ~1 hr.

Central Nervous System Effects

Animals were closely observed for signs of central nervous system toxicity (drowsiness, excitability, nystagmus, and convulsions). Logistic regression analysis (GLIM version 3.12: The Royal Statistical Society, London) was used to determine the relationship between the dose or maximum measured arterial blood concentrations of each drug and the probability of convulsions.

Cardiovascular and Hemodynamic Measurements

The animals were supported in a sling to facilitate calibration and baseline positioning of external pressure transducers (for the measurement of blood pressures) and to prevent injury should the animals develop local anesthetic-induced convulsions. Approximately 30 min was allowed for the sheep to settle before calibration of the recording equipment, prior to baseline measurements. Chart recordings of the hemodynamic parameters were obtained continuously for 10 min after drug administration. Cardiac output was determined approximately every 30 sec for the duration of the experiment. The signal from the pressure transducer in the left ventricle was differentiated and displayed on the chart recorder; the maximum rate of rise of left ventricular pressure (dP/dt_{max}) was observed as an index of myocardial contractility. Values of dP/dt_{max}, left ventricular end diastolic pressure (LVEDP) and mean arterial and pulmonary artery pressures (respectively, MAP and MPAP) were read at the same times as those designated for blood sampling. Each value for dP/dt_{max} was taken as the average of those during four successive cardiac cycles. The signals from the intracardiac ECG electrodes were amplified and displayed on the chart recorder. Heart rate (HR) was calculated after counting the number of cardiac cycles per 10-sec period. Systemic vascular resistance (SVR) was calculated from the difference between MAP and CVP divided by CO (and multiplied by 79.9 to give units of dyne·sec·cm^{-5}).

Intrapleural Pressure Measurements

Continuous chart recordings of intrapleural pressure were made in four animals during convulsions. At the time of vascular cannulation a trocar cannula (size 16 FR, Argyle Ltd., St. Louis, MO) was inserted under direct vision by way of a 3–4-cm incision with dissection down to the intercostal membrane. An underwater seal drain was used for the first 3–4 days postoperatively to prevent the development of pneumothorax. Intrapleural pressure was measured with a size 7F pressure transducer-tipped catheter (PC 350, Millar Instruments) inserted into the saline-filled cannula. The output of this transducer was displayed on the same chart recorder as the other variables.

Blood Samples for Acid–Base Determination

Arterial blood samples (1 mL) were obtained for measurements of blood gas tension and acid–base

Table 1. Local Anesthetic Doses Producing Convulsions

	Time of Onset of Convulsions (min)	Time of Offset of Convulsions (min)	Number of Animals Convulsing/ Number of Animals
Lidocaine (mg)			
150	0.8 ± 0.4	2.8 ± 1.3	6/6
200	0.8 ± 0.0	2.0 ± 0.0	2/2
320	0.5 ± 0.3	3.2 ± 0.5	5/5
Bupivacaine (mg)			
37.5	0.7	2.0	1/7
50	0.5 ± 0.2	2.6 ± 0.8	3/4
80	0.4 ± 0.2	3.4 ± 1.3	5/5
Ropivacaine (mg)			
60	0.5 ± 0.3	2.2 ± 1.6	3/5
90	0.5 ± 0.3	2.3 ± 1.0	7/7
120	0.6 ± 0.3	2.6 ± 1.3	5/5

Values expressed as means ± SD.

status before and at 2, 5, and 10 min after drug administration.

Blood Samples for Pharmacokinetic and Pharmacodynamic Analysis

After drug administration, serial arterial blood samples (0.2–0.5 mL) were obtained at ~0.25, 0.5, 0.75, 1.0, 1.5, and 2.0 min and then every minute for 10 min. Blood local anesthetic concentrations were determined by gas chromatography with nitrogen-selective detection after solvent extraction (14).

Results

Survival

All animals were in apparently good health and had normal acid–base and serum electrolyte status prior to the experiments. All animals survived all doses of lidocaine. At the greatest dose of bupivacaine (80 mg), two of the five animals died within 2 min of receiving this dose. With ropivacaine, one of seven animals died within 2 min of receiving 90 mg, as did one of five animals given 120 mg.

There were no hemodynamic or metabolic response to the "placebo" injections.

Central Nervous System Effects

No animals convulsed after lidocaine 80 mg, bupivacaine 20 mg, or ropivacaine 30 and 45 mg. After bupivacaine 37.5 mg, one of seven animals convulsed

Table 2. Baseline Hemodynamic Values before Drug Administration

	Lidocaine Group	Bupivacaine Group	Ropivacaine Group
HR (beats/min)	107 ± 19 (18)	110 ± 14 (21)	104 ± 14 (28)
LVEDP (mm Hg)	12 ± 5 (18)	11 ± 5 (21)	12 ± 4 (28)
dP/dt_{max} (mm Hg/sec)	2400 ± 450 (18)	2450 ± 450 (20)	2400 ± 350 (28)
MAP (mm Hg)	101 ± 15 (18)	101 ± 15 (21)	105 ± 9 (28)
MPAP (mm Hg)	14 ± 4 (18)	17 ± 3 (21)	17 ± 5 (28)
CO (L/min)	6.2 ± 1.2 (18)	6.1 ± 1.2 (21)	6.6 ± 1.4 (28)
SVR (dyne·sec·cm^{-5})	1356 ± 316 (18)	1407 ± 372 (21)	1270 ± 290 (28)

Abbreviations: HR, heart rate; LVEDP, left ventricular end diastolic pressure; dP/dt_{max}, maximum rate of left ventricular pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SVR, systemic vascular resistance.

Values expressed as mean ± SD; number of experiments in parentheses.

and three of four animals convulsed after 50 mg; after ropivacaine 60 mg, three of five animals convulsed. After doses of or >150 mg of lidocaine or 90 mg of ropivacaine, as well as after doses of 80 mg of bupivacaine, all animals convulsed for several minutes (Table 1).

The logistic regression equation describing the relationship between the dose and the probability of convulsions after intravenous bolus doses was:

$$\text{Logit } [P] = -64.24 + 8.38(r) + 12.24(b) + 13.72^*\ln (\text{dose}),$$
$$(3.80) \quad (4.84) \quad (4.29)$$

where Logit $[P] = \ln [P/(1 - P)]$, P = probability of convulsions, and ln = natural log, and where $r = 1$ if ropivacaine and 0 if not, and $b = 1$ if bupivacaine and 0 if not. The standard errors in the equation are given in parentheses underneath. In the calculation it was determined that the slopes were not significantly different and that in the equation the coefficients assigned to ropivacaine, bupivacaine, and dose were significantly different to zero ($P < 0.05$). From this equation the values of CD_{50} were ~110 mg for lidocaine HCl, 45 mg for bupivacaine HCl, and 60 mg for ropivacaine HCl.

Similarly, the equation describing the relationship between the maximum measured arterial blood drug concentration and the probability of convulsions after intravenous bolus doses was:

$$\text{Logit } [P] = -8.81 + 4.23(r) + 5.84(b) + 0.225^*\text{conc.}$$
$$(1.58) \quad (2.08) \quad (0.062)$$

From this equation, corresponding maximum measured arterial blood concentrations associated with a 50% probability of convulsions were, respectively, 40, 14, and 20 mg/L for lidocaine, bupivacaine, and ropivacaine.

Cardiovascular Effects

Because there was considerable variability between animals in the control values of SVR and dP/dt_{max}

(Table 2), the values after drug administration are presented as the means of the changes of percentage from baseline values in animals receiving the specified doses (Figures 1 and 2). For other measurements where there was little variability in baseline values, the results are expressed as the means of the absolute changes from baseline values.

After the lowest doses of each drug which did not produce convulsions (lidocaine 80 mg, bupivacaine 20 mg, and ropivacaine 30–45 mg), there were minimal cardiovascular changes (Figures 1 and 2).

With higher doses of each drug, there were increases in HR, MAP, MPAP, CO (exception 200 mg of lidocaine), SVR, LVEDP, and dF/dt_{max} (Figures 1 and 2) which were closely related to the time of onset of convulsions. In those animals that survived these doses, the cardiovascular parameters returned to near baseline values by 10 min after drug administration.

Effects of Convulsions on Intrapleural Pressure

The range of intrapleural pressure (IPP) changes during the respiratory cycle increased, but there was no increase in mean IPP during convulsions. The influence of these changes in intrapleural pressure was discernible on the LVEDP trace. However, LVEDP remained markedly elevated even during maximal inspiration.

Acid–Base Status

When local anesthetic doses produced convulsions, the animals hyperventilated and maintained a clear airway. The mean values of arterial blood pH at 2, 5, and 10 min after administration of each drug were not significantly different from baseline values, whether or not the animals convulsed (Table 3).

Figure 1. Effects of lidocaine, bupivacaine, and ropivacaine on heart rate, mean arterial blood pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR). Values plotted are the mean changes from control values in animals receiving each specified dose.
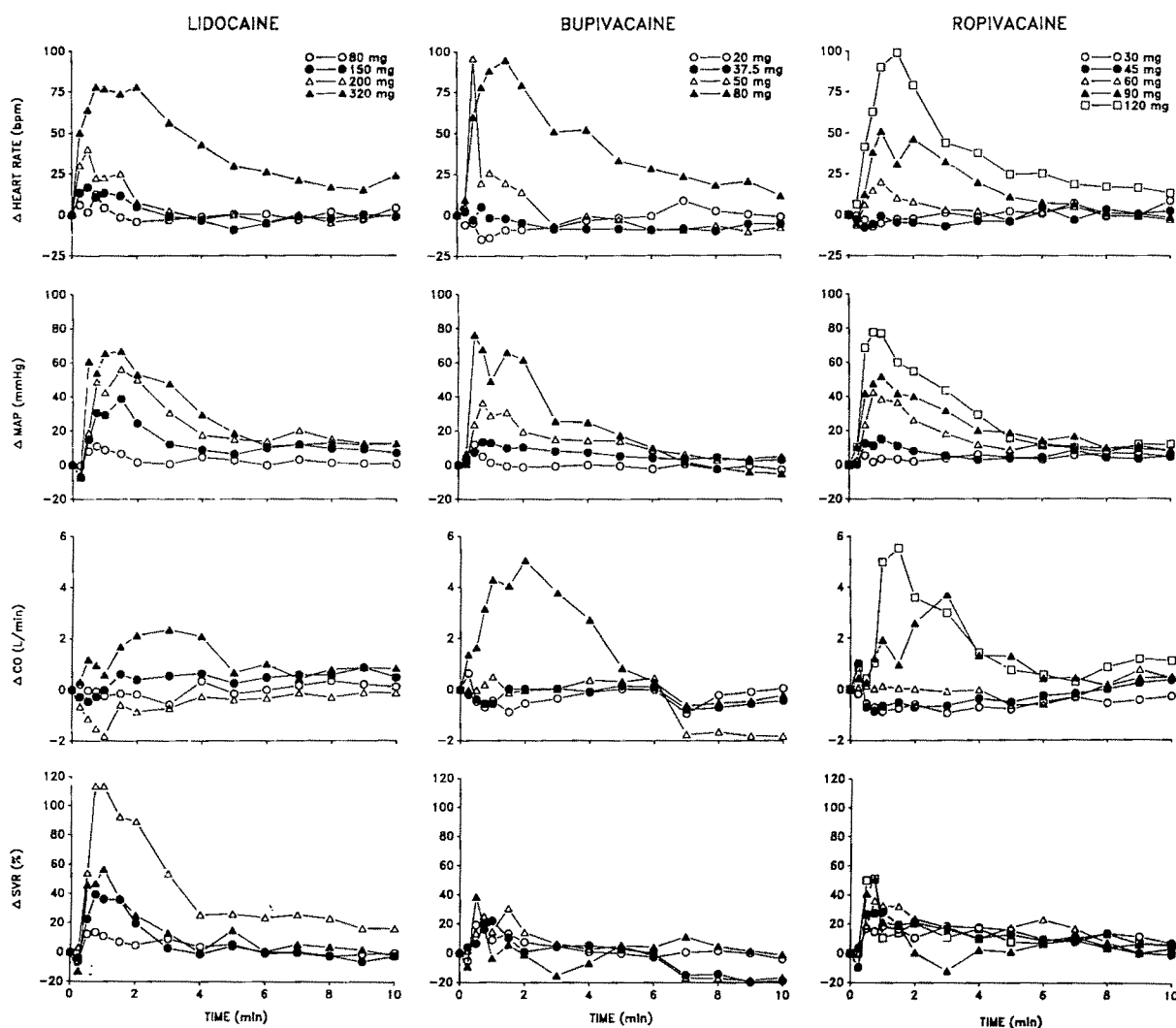
Blood Drug Concentrations

Arterial blood drug concentrations usually were maximal in the first blood sample and decreased rapidly. Therefore, the maximum concentrations measured in discrete samples were approximations of true maximal values because the rate of sampling was slow compared with the rate of change of blood concentrations. Although marked interstudy variability was noted in early (<1 min) concentrations of each drug, arterial blood bupivacaine and ropivacaine concentrations per 100 mg of dose after this time were similar and always greater than those of lidocaine, but there was no obvious trend towards dose dependency for any agent (Table 4).

Discussion

In this study design, single intravenous bolus doses of each agent were administered separately to simu-

late the clinical situation of inadvertent intravascular injection. This avoided any pharmacodynamic and pharmacokinetic uncertainties associated with prolonged infusion or repeated dose experimental designs. All experiments were performed in conscious animals to determine whole-body responses in the absence of general anesthetic agents.

It is of interest to compare the convulsive doses and blood concentrations of lidocaine and bupivacaine found in this study with values in the sheep reported by others, if only to highlight the influences of different experimental designs. Morishima and co-workers (15,16), for example, infused either lidocaine at 2 $mg \cdot kg^{-1} \cdot min^{-1}$ or bupivacaine at 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$ into adult sheep and found mean
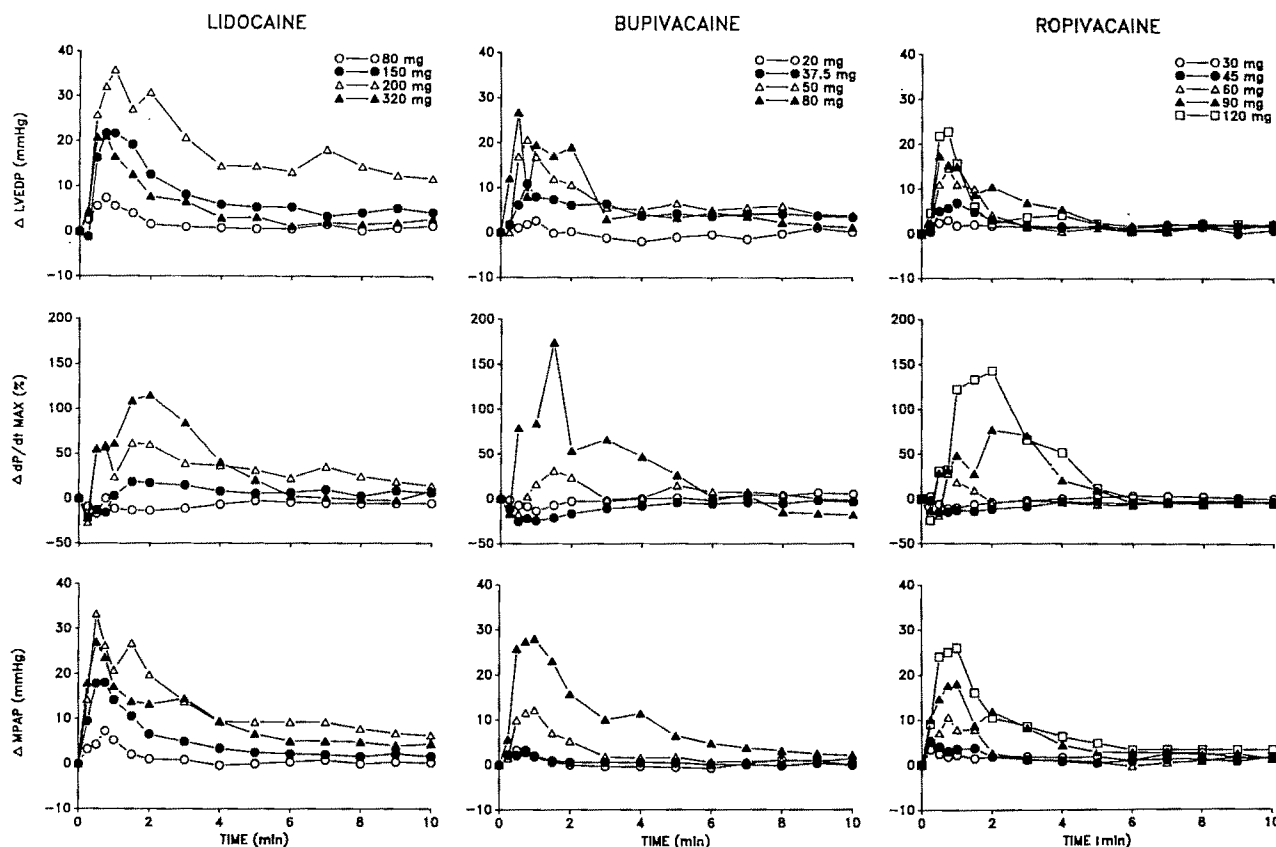
Figure 2. Effects of lidocaine, bupivacaine, and ropivacaine on left ventricular end diastolic pressure (LVEDP), dP/dt_{max} (as an index of myocardial contractility), and mean pulmonary arterial pressure (MPAP). Values plotted are the mean changes from control values in animals receiving each specified dose.

convulsive doses of 5.8 mg/kg (=301 mg) and 2.7 mg/kg (=111 mg), respectively. These values are about 2.5 times those found in the present study. The difference, it would appear, is related to the slower rate of administration in those studies (15,16), allowing more extensive redistribution of drug to less well perfused organs. Similarly, the "convulsive arterial blood concentrations" of lidocaine and bupivacaine in the present study were two to three times greater than those reported by Morishima et al. (15,16), apparently reflecting the disequilibrium between drug blood and tissue concentrations in the present study and emphasizing the inherent variability in such values under any but equilibrium conditions.

The ratios of values of convulsive doses (2.4:1.3:1) and of arterial blood concentrations (2.9:1.4:1) for lidocaine/ropivacaine/bupivacaine did not indicate that the CNS toxicities of bupivacaine or ropivacaine were disproportionate to their expected clinical dosages. If anything, the CNS toxicity of lidocaine is

disproportionately greater than that of its longer-acting congeners—a finding that has been attributed to its relatively lower plasma protein binding (17). Furthermore, it should be emphasized that the "convulsive arterial blood concentrations" under rapidly changing conditions are not adequately represented by peripheral venous blood concentrations often measured in clinical studies. The latter are damped by the rate of local tissue uptake and equilibration and are of any use only under conditions of slow change.

Convulsions initiated by the local anesthetic agents resulted in increases in HR, MAP, MPAP, CO, and SVR, suggesting that the responses may be mediated by the autonomic nervous system. Others have noted that similar cardiovascular changes during electrically or drug-induced convulsions were abolished by transection of the cervical spinal cord of anesthetized sheep (18). Hypertension during convulsions is abolished by α-adrenoceptor blockade, but not by bilateral adrenalectomy (19). Thus, a final common pathway appears to be the sympathetic nervous system. The overall results from the present study are consistent with those of hemodynamic investigations performed in dogs (20,21).

Table 3. Arterial Blood Gas Status 2, 5, and 10 min after Bolus Administration of Local Anesthetics

Group	Lidocaine-treated				Bupivacaine-treated				Ropivacaine-treated			
	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BE (mEq/L)	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BE (mEq/L)	pH	Pco$_2$ (mm Hg)	Po$_2$ (mm Hg)	BE (mEq/L)
Animals not convulsing												
Baseline	7.47	38.7	93.6	5.08	7.48	36.5	84.6	4.18	7.49	35.2	92.4	4.35
	±0.03	±4.4	±7.8	±1.20	±0.04	±0.8	±11.4	±2.67	±0.04	±3.7	±7.4	±2.49
Change from baseline												
2 min	−0.02	1.8	−3.6	−0.78	0.00	−0.5	6.8	−0.42	0.01	0.3	−2.4	0.44
	±0.07	±9.0	±2.1	±1.27	±0.02	±2.2	±8.2	±0.96	±0.04	±3.1	±7.1	±1.46
5 min	−0.01	−0.3	0.6	−0.88	−0.01	−0.04	6.5	−0.64	0.0	0.2	−0.7	0.02
	0.06	±6.9	±7.2	±1.15	±0.02	±2.5	±8.2	±1.02	±0.04	±3.6	±8.5	±1.55
10 min	0.0	−2.5	3.8	−0.98	−0.01	−0.4	4.5	−1.12	0.0	0.4	0.8	−0.73
	±0.05	±5.4	±5.9	±0.73	±0.01	±1.6	±2.2	±0.68	±0.04	±4.2	±6.9	±2.94
Animals convulsing after local anesthetic injection												
Baseline	7.49	36.3	98.4	5.26	7.52	33.5	101.3	5.47	7.49	35.9	92.1	5.12
	±0.02	±3.0	±8.4	±0.89	±0.04	±3.2	±4.0	±1.19	±0.04	±2.7	±10.4	±1.73
Change from Baseline												
2 min	−0.01	−1.3	−9.0	−1.50	−0.02	−1.3	−14.3	−1.77	0.01	−2.5	1.7	−1.06
	±0.07	±9.7	±16.6	±0.70	±0.03	±4.6	±21.2	±0.51	±0.07	±5.4	±15.3	±1.45
5 min	−0.03	0.9	−11.2	−1.34	−0.01	−3.4	−7.0	−3.07	0.01	−2.3	2.2	−1.37
	±0.02	±2.6	±11.7	±0.30	±0.05	±7.3	±16.1	±1.23	±0.06	±5.1	±8.0	±1.82
10 min	−0.02	−0.7	−5.0	−2.06	−0.04	−1.2	−9.0	−3.70	−0.01	−1.5	6.5	−1.83
	±0.02	±4.1	±6.6	±1.07	±0.04	±5.4	±17.1	±0.82	±0.04	±2.4	±10.0	±1.64

Abbreviation: BE, base excess.
Values are expressed as means ± SD.

Table 4. Arterial Blood Drug Concentrations per 100 mg of Dose

Drug Dose (mg)	Time (min)						
	1.0	1.5	2	3	4	5	10
	Blood Drug Concentration (mg/L)						
Lidocaine							
80 (n = 5)	4.9 ± 1.7	3.3 ± 1.0	2.7 ± 0.7	2.0 ± 0.3	1.5 ± 0.4	1.2 ± 0.2	0.68 ± 0.16
150 (n = 6)	12.9 ± 4.2	5.8 ± 2.7	3.5 ± 1.4	2.1 ± 0.4	1.5 ± 0.3	1.2 ± 0.2	0.61 ± 0.14
200 (n = 2)	11.0 ± 3.2	4.4 ± 2.0	3.2 ± 1.7	1.8 ± 0.7	1.7 ± 0.3	1.0 ± 0.2	0.64 ± 0.14
320 (n = 5)	6.5 ± 2.4	3.4 ± 0.7	2.5 ± 0.4	1.7 ± 0.3	1.5 ± 0.2	1.4 ± 0.6	0.73 ± 0.22
Bupivacaine							
20 (n = 5)	17.3 ± 6.8	10.7 ± 5.5	8.5 ± 3.8	6.3 ± 3.5	5.3 ± 2.5	4.2 ± 2.3	2.7 ± 1.5
37.5 (n = 7)	8.6 ± 3.5	5.2 ± 2.1	4.5 ± 1.8	3.8 ± 1.6	2.8 ± 1.2	2.5 ± 1.1	1.4 ± 0.7
50 (n = 3)	9.4 ± 5.7	4.4 ± 3.5	3.6 ± 2.7	3.0 ± 2.2	2.4 ± 1.8	2.1 ± 1.5	1.4 ± 1.2
80 (n = 5)	5.9 ± 3.9	4.4 ± 3.7	4.3 ± 3.9	3.5 ± 2.5	3.3 ± 2.8	3.5 ± 2.8	2.1 ± 2.2
Ropivacaine							
30 (n = 5)	12.3 ± 4.1	8.9 ± 4.1	7.9 ± 3.7	5.8 ± 3.3	4.8 ± 2.7	4.3 ± 2.5	2.8 ± 2.2
45 (n = 6)	7.8 ± 3.2	5.1 ± 1.7	4.3 ± 1.4	3.7 ± 1.1	2.4 ± 0.8	2.2 ± 0.7	1.6 ± 0.5
60 (n = 5)	7.8 ± 3.1	5.2 ± 2.0	4.7 ± 1.3	3.4 ± 1.3	3.0 ± 1.2	2.7 ± 1.1	1.7 ± 0.8
90 (n = 7)	8.7 ± 4.3	5.6 ± 3.0	4.7 ± 2.8	3.6 ± 1.9	3.1 ± 1.9	2.7 ± 1.9	1.9 ± 1.5
120 (n = 5)	7.3 ± 3.1	4.7 ± 2.0	3.8 ± 1.6	3.3 ± 1.6	3.0 ± 1.4	1.8 ± 0.4	1.9 ± 1.6

Values expressed as means ± SD.

There is evidence that local anesthetics also have additional direct actions on pulmonary vasculature (22) in addition to their autonomically mediated responses. It is not known whether the effects on pulmonary vessels occur in humans but the present findings corroborate findings of other studies of lidocaine and bupivacaine toxicity in both sheep (23) and dogs (20). In the present study there was, in surviving animals, no arterial hypoxemia (Po$_2$ < 70 mm Hg), suggesting that pulmonary hypertension was not associated with pulmonary ventilation/ perfusion abnormalities.

Apart from reflex effects during convulsions, CNS toxicity of lidocaine and bupivacaine may be associated with other effects on the cardiovascular system. The direct application of either lidocaine or bupivacaine to the exposed nucleus tractus solitarius of the rat brain (24) and lateral cerebral ventricle of cats (25) produces arrhythmias. The relationship of these findings and of the recent description of specific local anesthetic binding in brain tissue (26) to systemic drug administration is uncertain in the absence of data correlating the time-courses of regional (and preferably microregional) drug uptake with corresponding concentration–response data.

The marked elevations in LVEDP seen in the present study were unexpected. Possible causes for elevations in LVEDP include reduction in myocardial contractility, increase in systemic vascular resistance, reduction in myocardial compliance, or a combination of these factors (26). During experiments in which convulsions occurred, there were no decreases in dP/dt_{max} great enough to explain the observed substantial increases in LVEDP. However, large increases in SVR did occur which may have contributed to the elevated LVEDP (27,28). Acute right ventricular dilation with right to left shift of the intraventricular septum, leading to an acute reduction in left ventricular compliance, consequent to the increases in pulmonary vascular resistance, also may have contributed to the elevation in LVEDP.

In that it was considered possible that thoracic wall muscular hypertonicity during convulsions might increase mean intrathoracic pressure that, with transmission via thoracic structures, might in turn affect left ventricular and pulmonary artery pressures, intrapleural pressures were measured during local anesthetic-induced convulsions. No changes in mean intrapleural pressure were observed; all animals hyperventilated and maintained a clear airway. Therefore, changes in LVEDP were not caused by increases in intrathoracic pressure.

In summary, after intravenous doses of lidocaine, bupivacaine, and ropivacaine that did not produce convulsions, there were minimal cardiovascular changes. After doses that produced convulsions, there were marked increases in HR, MAP, CO, MPAP, SVR, LVEDP, and dP/dt_{max}. Within the putatively equi-anesthetic equivalent-to-clinical dose range studied in these experiments, there were no appreciable differences between the drugs with non-fatal doses. Of note is that one of the two sheep that died following bupivacaine (80 mg) and one sheep that died after ropivacaine (90 mg) had all survived a lidocaine (320 mg) bolus on a previous occasion, suggesting a disproportionately lower cardiotoxicity

of lidocaine compared with bupivacaine and ropivacaine. However, further studies are indicated to determine fatal doses, mechanisms of death and the myocardial and cerebral drug distributions of each of these agents.

References

1. Adams HJ, Kronberg GH, Takman B. Local anesthetic activity and acute toxicity of (±) -2-(N-ethylpropylamino)-2',6' - butyro-xylidide, a new long-acting local anesthetic. J Pharm Sci 1972;61:1829–31.

2. Jorfeldt L, Löfström B, Pernow 3, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesth Scand 1968;12:153–69.

3. Covino BG, Vassallo HG. Local anesthetics: mechanisms of action and clinical use. The scientific basis of clinical anesthesia. New York: Grune & Stratton, 1976.

4. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. Br J Anaesth 1975;47:213–24.

5. Tucker GT, Mather LE. Absorption and disposition of local anesthetics: pharmacokinetics. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: JB Lippincott, 1988:47–110.

6. Munson ES, Tucker WK, Ausinsch B. Malagodi MH. Etidocaine, bupivacaine, and lidocaine seizure thresholds in monkeys. Anesthesiology 1975;42:471–8

7. Malagodi MH, Munson ES, Embro MJ. Relation of etidocaine and bupivacaine toxicity to rate of infusion in Rhesus monkeys. Br J Anaesth 1977;49:121–5.

8. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.

9. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736–46.

10. Åkerman B, Hellberg IB, Trossvik C. Primary evaluation of the amino amide agent ropivacaine (LEA 103). Acta Anaesthesiol Scand 1988;32:571–8.

11. Runciman WB, Ilsley AH, Mather LE, Carapetis R, Rao MM. A sheep preparation for studying interactions between blood flow and drug disposition: I. Physiological profile. Br J Anaesth 1984;56:1015–28.

12. Blunt MH, Huisman THL. The haemoglobins of sheep. In: Blunt MH, ed. The blood of sheep. Berlin: Springer-Verlag, 1975:155–85.

13. Morishima HO, Finster M, Pedersen H, Fukunaga A, Ronfeld RA, Vassallo HG, Covino BG. Pharmacokinetics of lidocaine in fetal and neonatal lambs and adult sheep. Anesthesiology 1979;50:431–6.

14. Nancarrow C, Runciman WB, Mather LE, Upton RN, Plummer JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and brain of the sheep. Anesth Analg 1987;66:925–35.

15. Morishima HO, Pedersen H, Finster M, Sakuma K, Bruce SL, Gutsche BB, Stark RI, Covino BG. Toxicity of lidocaine in adult, newborn and fetal sheep. Anesthesiology 1981;55:57–61.

16. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur GR, Covino BG. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology 1985;63: 134–9.

17. Mather LE, Long GJ, Thomas J. The intravenous toxicity and clearance of bupivacaine in man. Clin Pharmacol Ther 1971; 12:935–43.

18. Bayne LL, Simon RP. Systemic and pulmonary vascular pressures during generalised seizures in sheep. Ann Neurol 1981; 10:566–9.

19. Doba N, Beresford HR, Reis DJ. Changes in regional blood flow and cardiodynamics associated with electrically and chemically induced epilepsy in cat. Brain Res 1975;90:115–32.

20. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22.

21. Liu P, Feldman HS, Giasi R, Patterson MK, Covino BG. Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg 1983;62:375–9.

22. Hyman AL. The effects of lidocaine, hexamethonium and alpha and beta adrenergic blocking agents on the pulmonary veins in intact dogs. J Pharmacol Exp Ther 1970;174:487–99.

23. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984;60:10–8.

24. Thomas RD, Behbehani MM, Coyle DE, Denson DD. Cardiovascular system toxicity of local anesthetics: an alternative hypothesis. Anesth Analg 1986;65:444–50.

25. Heavner JE. Cardiac dysrhythmias induced by infusion of local anesthetics into the lateral cerebral ventricle of cats. Anesth Analg 1986;65:133–8.

26. Braunwald B, Frahm CJ. Studies on Starling's law of the heart: IV. Observations on the hemodynamic functions of the left atrium in man. Circulation 1961;24:633–42.

27. Plum F, Howse DC, Duffy TE. Metabolic effects of seizures. Res Publ Assoc Res Nerv Ment Dis 1974;53:141–57.

28. White PT, Grant P, Mosier J, Craig A. Changes in cerebral dynamics associated with seizures. Neurology 1961;11:354–61.

Ventilatory and Cardiovascular Responses to Sufentanil Infusion in Dogs Anesthetized with Isoflurane

Imad H. Abdul-Rasool, MD, PhD and Denham S. Ward, MD, PhD

ABDUL-RASOOL IH, WARD DS. Ventilatory and cardiovascular responses to sufentanil infusion in dogs anesthetized with isoflurane. Anesth Analg 1989;69:300-6.

The ventilatory and hemodynamic responses to hypoxia, hyperoxia, and hypercapnia before and during sufentanil infusion were studied in 16 chronically tracheostomized dogs anesthetized with two concentrations, 1 and 0.5 minimal alveolar concentration (MAC) of isoflurane. Sufentanil was infused at a rate to obtain a constant end-tidal carbon dioxide ($P_{ET_{CO_2}}$) of ~50 mm Hg for each isoflurane level. Before the sufentanil infusion, the $P_{ET_{CO_2}}$ was increased to 50 mm Hg by adding CO_2 to the inspired gas, to allow comparisons at isocapnic conditions. Sufentanil caused only minor hemodynamic changes but significantly reduced ventilation during both levels of isoflurane. The ventilatory response to hypercapnia decreased substantially, but there were no significant alterations in the ventilatory response to hypoxia. After sufentanil infusion, hyperoxia caused a larger decrease in minute ventilation and caused apnea in four dogs. These results suggest that administering sufentanil during isoflurane anesthesia causes a reduction in the contribution of the central chemoreflexes to ventilatory drive and, consequently, a relative increase in the contribution from the peripheral chemoreflexes.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANALGESICS—sufentanil. VENTILATION—isoflurane plus sufentanil.

The short-acting narcotic, sufentanil, is frequently administered to smooth the induction of anesthesia and lessen unwanted hemodynamic responses to intubation. It is also used as an anesthetic supplement to provide analgesia and to reduce the patient's requirements for potent inhalational anesthetics (1,2). During the emergence period, sufentanil can minimize the hemodynamic alterations associated with awakening and extubation. Although it is important to prevent these hemodynamic changes during the emergence period, it is equally important to allow the patient to breathe spontaneously and to maintain an adequate ventilation.

Sufentanil produces minimal cardiovascular changes under normoxic normocapnic conditions (3). Although hypoxemia can potentially occur during emergence, whether or not the cardiovascular responses to hypoxemia are altered by narcotics in spontaneously breathing subjects is not well documented. The ventilatory effects of inhalation anesthetics and narcotics separately are well known, but the ventilatory effects of the combination have not been described. Since both drugs depress ventilation through actions on central and peripheral chemoreflexes (4–8), there may be synergistic effects that would depress spontaneous ventilation during the preemergence period and delay the onset of adequate ventilation.

In dogs, we combined an infusion of sufentanil with two levels of isoflurane (end-tidal isoflurane levels of ~1 and 0.5 minimal alveolar concentration [MAC]). The initial dose of sufentanil and the infusion rate were chosen to produce a steady level of end-tidal carbon dioxide (CO_2) of 50 mm Hg so that the hemodynamic and respiratory responses could be assessed at isocapnic conditions during both levels of isoflurane anesthesia. The ventilatory response was assessed using hypercapnia and hypoxic tests, and the cardiovascular response was assessed with hypoxemia.

Methods

Sixteen chronically tracheotomized mongrel dogs weighing 21 ± 0.8 kg (mean $\pm$ SD) were studied. Anesthesia was induced with isoflurane in air and

maintained through a cuffed tracheostomy tube. The body temperature was maintained constant (37–38°C) by means of a warming blanket and heating lamps. A percutaneous venous catheter was inserted in the forelimb, and normal saline was infused at a rate of 5 $mL \cdot kg^{-1} \cdot hr^{-1}$. An arterial line was placed percutaneously into the femoral artery for blood sampling and continuous monitoring of arterial pressure (AP). In seven dogs, a flow-directed balloon-tipped pulmonary artery catheter was inserted via the external jugular vein for measurements of right atrial (RA), pulmonary artery (PA), and pulmonary artery occlusion (PCWP) pressures and cardiac output (CO). The position of the catheter was guided by using the pressure readings. Blood pressures were measured with strain gauge transducers (model 1290 A, Hewlett-Packard Co., Andover, MA) calibrated with a mercury manometer. The CO was determined in triplicate by a thermodilution technique, using a cardiac output computer (model 78231C, Hewlett-Packard Co.).

Arterial and mixed venous blood samples (2 mL) were drawn anaerobically and analyzed in duplicate for Po_2, Pco_2, and pH using a calibrated pH/blood gas analyzer (System 1303, Instrumentation Laboratory, Inc., Lexington, MA).

Airway O_2, CO_2, N_2, and isoflurane concentrations were measured continuously using a mass spectrometer (1100 MGA, Perkin-Elmer Corp., Norwalk, CT) calibrated with a known gas mixture. An impeller flowmeter (Sensormedics, VMM-110 Laguna Hills, CA) which was calibrated with a pump, measured expired and inspired air flow. All continuously measured pressures, gas concentrations, and flows were sampled at 50 Hz and collected by an LSI-11 computer system (Digital Equipment Corporation, Marlboro, MA). The respiratory variables were determined on a breath-by-breath basis, and other variables were digitally averaged over a single breath. A stabilization period of ~1 hr was allowed after preparation was completed.

Three drug conditions were studied: first, 1 MAC isoflurane only; second, 1 MAC isoflurane plus sufentanil, and third, 0.5 MAC isoflurane plus sufentanil. The sufentanil was administered as an initial bolus over 5 min and then as a subsequent infusion that was titrated so the PET_{CO_2} was constant at 50 mm Hg. For the 0.5 MAC isoflurane condition, the sufentanil infusion was increased to maintain the constant PET_{CO_2}, while the isoflurane concentration was decreased. The drug conditions were studied in the same sequence on a single day in each dog. All 16 dogs were studied with 1 MAC isoflurane followed by 1 MAC isoflurane plus sufentanil, and in 9 of the

dogs, after the 1 MAC isoflurane plus sufentanil tests, the 0.5 MAC isoflurane plus sufentanil measurements were performed. A stabilization period of at least 1 hr was allowed after a change in drug conditions.

The experimental protocol consisted of achieving a steady-state period of ~30 min for each drug condition as judged by the end-tidal isoflurane, PET_{CO_2}, heart rate (HR), and AP. After this period, steady-state hemodynamic, and respiratory measurements were averaged over a period of 5 min, and arterial blood gas analysis was made. This was then followed sequentially by testing hyperoxic, hypercapnic, and hypoxic responses. A period of at least 10 min was allowed between each test. The hyperoxic test was performed only in the nine dogs who were studied under all three drug conditions.

The hyperoxic ventilatory response was assessed by averaging the ventilatory measurements over a period of 5 min, after allowing the dog to breathe ~100% O_2 for several minutes prior to the measurement period. The hypercapnic ventilatory response was assessed using a Read rebreathing technique (9). Rebreathing bags were filled with 6 L of a gas mixture of 7% CO_2 in O_2. Sufficient isoflurane was added to keep end-tidal constant at its pretest concentrations. The PET_{CO_2} during the rebreathing test ranged from 50 to 70 mm Hg. The hypoxic ventilatory response was assessed by changing the air-isoflurane mixture to an O_2–N_2–isoflurane mixture to obtain a PET_{O_2} of ~150 mm Hg. The PET_{O_2} was then reduced gradually over 10 min, by increasing the inspired N_2 concentration until a PET_{CO_2} of ~32 mm Hg was reached. The PET_{CO_2} was maintained constant at 50 mm Hg throughout the hypoxic challenge by manually adding CO_2 to the inspired gas mixture. For the isoflurane experiments without sufentanil, this PET_{CO_2} was achieved by adding CO_2 to the inspired gas mixture so that a steady PET_{CO_2} of 50 mm Hg was achieved for at least 30 min prior to the hypoxic test. Thus, all hypoxic responses were measured at a comparable PET_{CO_2} (10). The end-tidal isoflurane concentration was also maintained constant at 1 or 0.5 MAC, as appropriate, throughout the hypoxic test. A blood gas sample was obtained at the conclusion of each hypoxic test.

The following hyperbolic model was fitted to the measured V_I–PET_{O_2} data by least-squares regression:

$$V_I = \frac{A}{PET_{O_2} - C} + V_0. \quad (1)$$

The V_I–PET_{O_2} response is parameterized in terms of ventilation in hyperoxia, V_0; the Po_2 asymptote, C; and a shape factor of the hyperbolic curve, A (10).

Table 1. Steady-State Cardiovascular Data in Seven Dogs under 1 Minimal Alveolar Concentration Isoflurane before and during the Sufentanil Infusion

	1 MAC Iso alone (normoxia)	1 MAC Iso plus CO_2 (normoxia)	1 MAC Iso plus CO_2 (hypoxia)	1 MAC Iso plus Su (normoxia)	1 MAC Iso plus Su (hypoxia)
PET_{CO2} (mm Hg)	36 ± 2.7	51 ± 2[a]	50 ± 3.4[a]	50 ± 0.5[a]	48 ± 3.0[a]
$Paco_2$ (mm Hg)	40.0 ± 4	50.0 ± 2[a]	48 ± 4[a]	52 ± 4[a]	50 ± 3[a]
Pao_2 (mm Hg)	81 ± 10	95 ± 15	33 ± 8[a]	59 ± 8[a]	33 ± 5[a]
HR (beats/min)	123 ± 15	119 ± 14	129 ± 10	108 ± 9[a]	146 ± 22[a]
CO (L/min)	3.8 ± 1.1	4.6 ± 1.1	5.9 ± 1.4[a]	4.6 ± 1.3	6.7 ± 1.4[a]
SV (mL)	32 ± 10	39 ± 12[a]	46 ± 10[a]	43 ± 11[a]	47 ± 13[a]
MAP (mm Hg)	89 ± 20	85 ± 16	103 ± 11	70 ± 7[a]	91 ± 16
SVR (dynes·sec·cm^{-5})	1866 ± 701	1492 ± 543[a]	1367 ± 382[a]	1185 ± 319[a]	1029 ± 201[a]
MPAP (mm Hg)	14 ± 1.2	16 ± 1.6[a]	26 ± 2.2[a]	16 ± 2.9	24 ± 4.9[a]
PVR (dynes·sec·cm^{-5})	143 ± 61	136 ± 40	271 ± 79[a]	188 ± 44[a]	203 ± 67[a]
PCWP (mm Hg)	7.0 ± 2.6	8.7 ± 1.0	8.4 ± 4.5	5.4 ± 3.2	8.1 ± 1.7
CVP (mm Hg)	4.8 ± 1.0	5.3 ± 1.4	6.3 ± 1.6	5.7 ± 2.1	5.9 ± 2.1
$Cao_2–CVo_2$	2.1 ± 0.4	1.7 ± 0.2	1.6 ± 0.1	2.1 ± 0.2	1.5 ± 0.1
Do_2 (mL/min)	584 ± 34	710 ± 29[a]	540 ± 3.0	578 ± 32	547 ± 32
Do_2/Vo_2	4.2 ± 0.4	5.5 ± 0.2[a]	3.9 ± 0.3	3.4 ± 0.2	3.9 ± 0.3

The cardiovascular abbreviations are explained in the text. Iso, isofluorane; Su, sufentanil.
[a] $P = < 0.05$ as compared with 1 MAC Iso alone.

The value for C was estimated from each set of data, since an assumption of a fixed value may not be valid for drug studies. A simple transformation of the data was introduced by translating the origin, to the intersection of the asymptotes and applying a 45° clockwise rotation of the coordinate system so that an accurate estimate of C, A, and V_0 values for each curve could be made.

The hypercapnic ventilatory response was fitted by a straight line using least-squares regression:

$$V_I = S (PET_{CO_2} - I). \qquad (2)$$

The parameters S and I are the slope and intercept of the CO_2 response curve, respectively.

The derived cardiovascular parameters were calculated using conventional equations and the O_2 consumption (Vo_2) was calculated using the Fick equation.

Analysis of variance for repeated measures with Bonferroni's t-test was used for statistical analysis using the BMDP statistical computer program (BMDP Software, Los Angeles, CA). A P value <0.05 was considered statistically significant. All data are given as mean ± SD.

Results

Sufentanil Infusion

The initial bolus was based on the weight of the dog and the subsequent infusion was adjusted based on the PET_{CO_2}. In all 16 dogs, the bolus averaged 12.7 ±

6.5 µg/kg and the average infusion rate was 0.01 ± 0.002 µg·kg^{-1}·min^{-1} during 1 MAC isoflurane. For the nine dogs that received all three treatments, the bolus was 14.0 ± 8.9 µg/kg and the infusion rate was 0.02 ± 0.008 µg·kg^{-1}·min^{-1} during 0.5 MAC isoflurane.

Cardiovascular Changes

The hemodynamic measurements are given in Table 1. The addition of inspired CO_2 during isoflurane to raise the PET_{CO_2} to 50 mm Hg produced significant changes in stroke volume (SV), systemic vascular resistance (SVR), mean pulmonary artery pressure (MPAP), oxygen delivery (CO × arterial O_2 content, $Cao_2)(Do_2)$, and O_2 availability ratio (Do_2/Vo_2). During the sufentanil infusion with a comparable PET_{CO_2}, there was an increase in SV and pulmonary vascular resistance (PVR), and a decrease in HR, mean arterial pressure (MAP), and SVR as compared with that during isoflurane plus CO_2 period. There were no significant changes in the arterial-mixed venous oxygen content difference, ($Cao_2 - Cvo_2$) and central venous pressure (CVP) throughout the study period. The hypoxic challenge during isoflurane alone produced significant increases in CO, SV, MPAP, and PVR with significant decrease in SVR. During isoflurane plus sufentanil infusion, similar changes were observed except a significant increase in HR. The cardiovascular responses, during the hypoxic challenge before and during sufentanil infusion, were not significantly different.

Table 2. Steady-State Ventilatory Measurements for the Three Drug Conditions

	1 MAC Iso alone plus CO_2 (normoxia)	1 MAC Iso plus Su (normoxia)	0.5 MAC Iso plus Su (normoxia)
V_I (L/min)	6.3 ± 2.5	2.6 ± 1.0^a	$2.8 \pm 0.8^{a,b}$
V_T (mL)	447 ± 146	339 ± 158^a	$243 \pm 112^{a,b}$
F (min^{-1})	14 ± 6	8 ± 5^a	11 ± 5
PET_{CO_2} (mm Hg)	51 ± 2	50 ± 2	49 ± 3.5
PET_{O_2} (mm Hg)	111 ± 6	82 ± 14^a	81 ± 8^a
$Paco_2$ (mm Hg)	51 ± 4	55 ± 5^a	54 ± 3.0
PaO_2 (mm Hg)	99 ± 12	62 ± 9^a	67 ± 6^a
pH	7.22 ± 0.03	7.19 ± 0.04^a	7.21 ± 0.03
N	16	16	9

The ventilatory abbreviations are defined in the text. Iso, isoflurane; Su, sufentanil. The data were obtained under normonic conditions for all three conditions.

[a] $P < 0.05$ as compared with Iso alone.
[b] $P < 0.05$ as compared with 1 MAC Iso + Su.

Respiratory Changes

Table 2 gives the steady-state ventilatory measurements for the three drug conditions. The results are presented for the combined data, but the statistical comparisons were used only in the dogs common to the groups being compared. The bolus and infusion of sufentanil caused significant changes in V_I, tidal volume (V_T), respiratory rate (F), PET_{O_2}, Pao_2, $Paco_2$, and pH during 1 MAC isoflurane, but the V_I and F partially recovered during 0.5 MAC isoflurane plus sufentanil.

Figure 1 shows the composite CO_2 response curves along with the parameter values. During the sufentanil infusion, two dogs became apneic after taking two breaths of the hyperoxic gas mixture contained in the rebreathing bags. The CO_2 rebreathing test was not conducted in these dogs and their responses prior to the infusion were not included in the statistical analysis. The addition of sufentanil caused a significant decrease in the CO_2 response slope. Decreasing the isoflurane and increasing the sufentanil infusion did not cause any further significant change in the slope. During 1 MAC isoflurane plus sufentanil and 0.5 MAC isoflurane plus sufentanil the slopes of the CO_2 response curves were not significantly different from zero.

Figure 2 shows the composite hypoxic response curves along with the parameter values. Only the ventilatory asymptote V_0 changed significantly with the sufentanil infusion. The hyperbolic shape parameter, A, and the hypoxic asymptote, C, did not change significantly. Although the steady-state measurements showed that the 1 MAC isoflurane plus sufentanil condition had a higher $Paco_2$, blood gas

tensions at the end of the hypoxic period were not significantly different from each other (Table 2).

In nine dogs (see Methods setion), hyperoxia caused a small, but significant decrease in ventilation (5.0 ± 0.9 to 4.5 ± 0.7 L/min) during 1 MAC isoflurane alone. After the sufentanil infusion was started, hyperoxia caused two dogs to become apeic. In the remaining dogs, hyperoxia caused a larger reduction in ventilation, from 2.2 ± 0.5 to 1.6 ± 0.5 L/min in the 1 MAC plus sufentanil condition ($P < 0.05$) and from 2.8 ± 0.8 to 1.9 ± 0.8 L/min in the 0.5 MAC plus sufentanil condition ($P < 0.05$).

Discussion

The cardiovascular changes caused by the introduction of hypercapnia during isoflurane anesthesia were consistent with those reported by others (11,12). These changes primarily reflected a peripheral vasodilation and an increase in CO. During sufentanil infusion, the increase in pulmonary vascular resistance was most likely due to a lower Pao_2. While the sufentanil infusion lowered HR and MAP, there was still an appropriate increase in both during hypoxic stress. Although it is desirable to reduce the unwanted hemodynamic responses to stress, during hypoxia it is also important to achieve hemodynamic changes that can maintain the balance between O_2 supply and demand. The increase in CO and subsequently in O_2 delivery seen during sufentanil infusion was able to maintain the balance between O_2 flux and demand as judged by unchanged $Cao_2 - Cvo_2$ and Do_2/Vo_2 during the hypoxic challenge. The results indicate that the addition of sufentanil to isoflurane did not blunt the appropriate hemodynamic reflexes to hypoxic stress.

It is well known that inhalational anesthetics depress ventilation as evidenced by a decrease in V_I and an increase $Paco_2$ (4,5). In addition, isoflurane blunts the ventilatory response to hypercapnia and hypoxia in both dogs and human beings (4-7). However, there is a marked difference in the degree of depression between humans and dogs. In humans, one MAC isoflurane substantially decreases the ventilatory response to hypercapnia and essentially abolishes the response to hypoxia (7). The effect of isoflurane on the ventilatory response to hyperoxia has not been described. In this study and others (4,5), during steady-state isoflurane anesthesia, dogs still exhibit an increase in ventilation in response to hypercapnia and hypoxia, although it presumably decreased in comparison to awake responses (4). The hypoxic response was comparable to those reported

DRUG	SLOPE	INTERCEPT
Iso	0.44 ± 0.26	35 ± 5
Iso + Su	0.08 ± 0.14*	37 ± 96
0.5 Iso + Su	0.05 ± 0.09*	46 ± 190
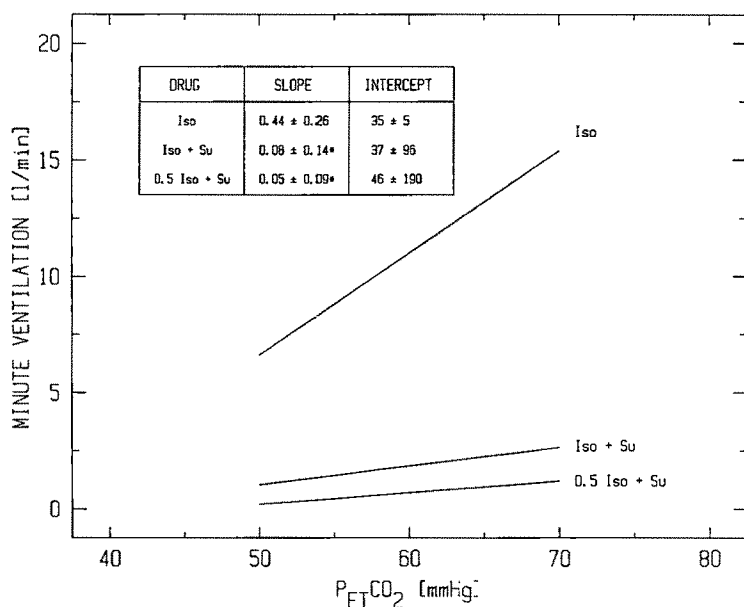
Figure 1. Composite ventilatory response to hypercapnia. The drug conditions are abbreviated as follows: Iso indicates 1 MAC isoflurane alone, Iso + Su indicates 1 MAC isoflurane plus sufentanil infusion, and 0.5 Iso + Su indicates 0.5 MAC isoflurane plus sufentanil infusion *P < different from 1 MAC isoflurane alone. $n = 14$ for Iso and Iso + Su and $n = 9$ for 0.5 Iso + Su (see text).

DRUG	A	Vo	C	PaO2	PaCO2
Iso	113.3 ± 112.6	5.4 ± 2.0	29.9 ± 8.6	33 ± 5	49 ± 3
Iso + Su	102.9 ± 77.5	1.4 ± 1.1*	26.4 ± 4.7	32 ± 4*	51 ± 4
0.5 Iso + Su	83.1 ± 36.7	2.2 ± 1.1*	26.2 ± 6.1	31 ± 3*	51 ± 4
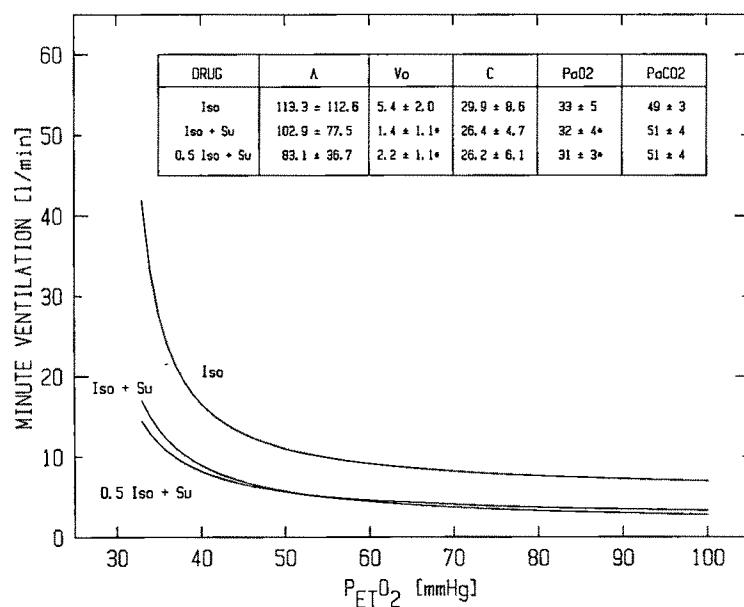
Figure 2. Composite ventilatory response to hypoxia. See Figure 1 for explanation of the abbreviation of drug conditions. The parameters A, V_3, and C refer to Eq. 1 in the text. The blood gas values were obtained at the end of the hypoxic test; $n = 16$ for Iso and Iso + Su and $n = 9$ for 0.5 Iso + Su (see text).

by Hirshman et al. (4) at similar $P_{ET_{CO_2}}$, but the average slope of the CO_2 response curves found in our study was larger. Differences in isoflurane concentration during the rebreathing period may exist between the two studies. We maintained the end-tidal isoflurane constant, while the isoflurane level was not reported by Hirshman and associates during this period.

It has been repeatedly shown that narcotics depress the hypercapnic ventilatory response in humans (13). Knowledge of the effects of narcotics on the hypoxic ventilatory response is more limited, with only two studies on the effects of narcotics (morphine in both studies) on the ventilatory response to hypoxia in human beings. Weil et al. (8) found that 7.5 mg of morphine given subcutaneously to healthy volunteers significantly depressed the hypoxic ventilatory response sixty minutes after its injection. Similar findings were observed by Santiago and his co-workers (14). Most of the drugs, including narcotics (6) that cause respiratory depression in humans, produce similar effects, although with differences in magnitude, in dogs (4–7,14).

The dog may be relatively resistant to the ventilatory depressant effects of opiates. The total dose used in this study is much larger than the dose in humans that would cause a comparable degree of hypercapnia. To account for these differences in pharmacody-

namics, we used a constant infusion with end-tidal CO_2 as the end point. This allowed us to define an end point for the dose ($P_{ET_{CO_2}}$ = 50 mm Hg) that is comparable to the degree of hypercapnia frequently seen in anesthetized patients during spontaneous breathing.

The effect of opiates on the hypoxic ventilatory response in dogs has been studied with inconclusive results. Bretschneider and Arndt (15) demonstrated that high doses of fentanyl (cumulative dose of 167.5 μg/kg over 25 min) in unanesthetized dogs in hyperoxia (Pa_{O_2} > 300 mm Hg) caused more respiratory depression and apneic episodes than did the same dose in ambient air. Our results agree with their conclusion that intact hypoxic ventilatory drive is important in maintaining ventilation after fentanyl administration. This does, however, contradict a conclusion in their earlier paper that hypoxic drive is not necessary (16).

In this study, the addition of sufentanil to isoflurane anesthesia caused a significant reduction in V_I and an increase in $P_{ET_{CO_2}}$ and Pa_{CO_2}. The decrease in V_I was due to decreases in both F and V_T. Although an attempt was made to maintain isocapnia as judged by the end-tidal CO_2, the 1 MAC isoflurane plus sufentanil condition had a significantly higher arterial CO_2. The widening of both the ET–aO_2 and the ET–aco_2 gradients after sufentanil indicates some worsening of the V/Q distribution in the lung. This could be a reflection of the increased PVR and the decreased ventilation after sufentanil. The hypercapnic ventilatory response during sufentanil infusion was significantly reduced. The slopes of the CO_2 response curves approached zero during 1 and 0.5 MAC isoflurane plus sufentanil (Figure 1). Therefore a wide variation and consequently a large SD were obtained when x-axis intercepts were calculated ($I_{y\text{-axis}} = I_{y\text{-axis}}/S$). This makes it difficult to draw a meaningful conclusion from the intercepts values.

The increases in ventilation in response to isocapnic hypoxia and hyperoxic hypercapnia are mediated, respectively, mainly via peripherally (carotid and aortic bodies in dogs) and centrally (medulla) located chemoreceptors. The central chemoreflexes are the main contributors to the ventilatory drive, while the peripheral chemoreflexes contributes ~20% under normoxic conditions. In humans, one MAC anesthesia blunts significantly the central and almost abolishes the peripheral chemoreflexes (7). The contribution of the peripheral chemoreflexes becomes even less important during inhalation anesthesia in humans. In dogs, however, one MAC isoflurane reduced the contribution of the peripheral chemoreflexes by ~50% (4). Our hyperoxic and hypoxic

results supported these findings. The dogs in this study still showed a significant increase in V_I in response to hypoxia, and a significant decrease in response to hyperoxia, indicating that the peripheral chemoreflexes were still functioning. Adding sufentanil to isoflurane caused insignificant changes in the ventilatory response to hypoxia whereas there was a larger reduction in V_I in response to hyperoxia both during one MAC isoflurane plus sufentanil and 0.5 MAC isoflurane plus sufentanil. In addition, four dogs became apneic when $P_{ET_{O_2}}$ was >300 mm Hg (the start of the CO_2 response and hyperoxic test), but did not when the Po_2 was ~150 mm Hg (the start of hypoxic test).

These results demonstrate that adding sufentanil to isoflurane anesthesia in dogs either causes no effect on the role of the peripheral chemoreflexes, or the role of these reflexes becomes more prominent. Our findings show that decreasing the drive from the peripheral chemoreceptors by hyperoxia causes either apnea or marked reduction in V_I making the second possibility more likely. It is also possible that sufentanil modified the direct hypoxic central depression. If the hypoxic central depression was decreased by sufentanil, then one would expect an augmentation of the ventilatory response to hypoxia and vice versa. Our data show no significant changes in the ventilatory response to hypoxia, suggesting that sufentanil produced no effect on the hypoxic central depression.

It must be emphasized that these results obtained in dogs should not be extrapolated to humans without reservations, especially when there is additional respiratory drives (e.g., pain, shivering) that are unrelated to the chemoreflexes. In humans, isoflurane leaves little peripheral drive and the addition of sufentanil may depress the central drive enough to inhibit adequate spontaneous ventilation. The combination of sufentanil and isoflurane in patients may require increased vigilance and monitoring in the recovery period.

References

1. Murphy MR, Hug CC. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982;57:785-8.

2. Hall RI, Murphy MR, Hug CC. The enflurane sparing effect of sufentanil in dogs [abstract]. Anesthesiology 1986;65:A551.

3. Reddy P, Liu WS, Port D, et al. Comparison of hemodynamic effects of anaesthetic doses of alphaprodine and sufentanil in the dog. Can Anaesth Soc J 1980;27:345–50.

4. Hirshman CA, McCullough RE, Cohen PJ, et al. Depression of hypoxic ventilatory response by halothane, enflurane and isoflurane in dogs. Br J Anaesth 1977;49:957–63.

5. Fourcade HE, Stevens WC, Larson CP. The ventilatory effects of Forane, a new inhaled anesthetic. Anesthesiology 1971; 35:26–31.

6. Hug CC, Murphy MR. Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. Anesthesiology 1979;50:342–9.

7. Knill RL, Kieraszewicz HT, Dodgson BG, et al. Chemical regulation of ventilation during isoflurane sedation and anaesthesia in humans. Can Anaesth Soc J 1983;30:607–14.

8. Weil JV, McCullough RE, Kline JS, et al. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. N Engl J Med 1975;292:1103–6.

9. Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. Australas Ann Med 1966;16:20–32.

10. Weil JV, Bryrne-Quinn E, Sodal IE, et al. Hypoxic ventilatory drive in normal man. J Clin Invest 1970;49:1061–71.

11. Cromwell TH, Stevens WC, Eger EI. et al. The cardiovascular effects of compound 469 (Forane) during spontaneous ventilation and CO_2 challenge in man. Anesthesiology 1971;35:17–25.

12. Price HL. Effect of carbon dioxide on the cardiovascular system. Anesthesiology 1960;21:652–61.

13. Keats AS. The effect of drugs on respiration in man. Annu Rev Pharmacol Toxicol 1985;25:41–65.

14. Santiago TV, Johnson J, Riley DJ, et al. Effects of morphine on ventilatory response to exercise. J Appl Physiol 1979;47:112–8.

15. Bretschneider H, Arndt JO. Breathing oxygen enhances fentanyl's respiratory depressant action in unanesthetized dog [abstract]. Anesthesiology 1986;65:A494.

16. Arndt JO, Mikat M, Parasher C. Fentanyl's analgesic, respiratory and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 1984; 61:355–61.

Lack of Effect of Spinal Anesthesia on Drug Metabolism

Edmund Whelan, MB, ChB, FFARCS, Alastair J. J. Wood, MB, ChB, FRCP, Sheila Shay, BS, and Margaret Wood, MB, ChB, FFARCS

The effect of spinal anesthesia on drug disposition was determined in six dogs with chronically implanted vascular catheters using propranolol as a model compound. On the first study day, 40 mg of unlabeled propranolol and 200 μCi of [^{3}H]propranolol were injected into the portal and femoral veins respectively. Arterial blood samples were taken for 4 hr for measurement of plasma concentrations of labeled and unlabeled propranolol by high-pressure liquid chromatography [HPLC] and of [^{3}H]propranolol by liquid scintillation counting of the HPLC eluant corresponding to each propranolol peak. Twenty-four hr later, spinal anesthesia was induced with tetracaine (mean dose 20.7 ± 0.6 mg) with low sacral to midthoracic levels and the propranolol infusions and sampling were then repeated. Spinal anesthesia had no significant effect on either the intrinsic clearance of propranolol (2.01 ± 0.75 L/min before and 1.9 ± 0.7 L/min during spinal anesthesia), or on mean hepatic plasma flow (2.01 ± 0.5 L/min before and 1.93 ± 0.5 L/min during spinal anesthesia). The systemic clearance and elimination half-life of propranolol were also unchanged by spinal anesthesia (0.9 ± 0.23 L/min on the first day, 0.7 ± 0.1 L/min during spinal anesthesia; and 101 ± 21 min on the first day, 115 ± 16 min during spinal anesthesia, respectively). The volume of distribution (Vd) of propranolol was similarly unaffected by spinal anesthesia. Thus the intrinsic clearance of propranolol, which reflects the drug metabolizing capacity of hepatic enzymes, was unchanged by spinal anesthesia. Over the 4-hr study period, there was no decrease in hepatic plasma flow, which, combined with the unchanged drug metabolism, resulted in no change in systemic clearance or elimination half-life. We therefore conclude that spinal anesthesia has no effect on propranolol metabolism under these circumstances; this is in contrast to the effects of halothane, enflurane, isoflurane, fentanyl, and propofol, all of which inhibit hepatic drug metabolism.

Key Words: BIOTRANSFORMATION, PROPRANOLOL—spinal anesthesia. ANESTHETIC TECHNIQUES—spinal. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—propranolol.

It is now well recognized that both surgery and anesthesia cause profound changes in perioperative drug disposition. There are four principal mechanisms by which anesthestics might affect drug disposition: 1) they may alter drug absorption; 2) they may alter drug distribution, by, for example, changing drug binding to plasma proteins; 3) they may alter hepatic blood flow; and 4) they may alter the activity of the liver enzymes responsible for drug metabolism. Previous studies have shown not only that both volatile anesthetics and intravenous agents inhibit drug metabolism, but also that changes in hepatic blood flow induced by anesthetic agents and techniques may contribute to altered drug clearance during anesthesia. Thus, halothane, enflurane, and nitrous oxide reduce liver blood flow both in animals (1–4) and humans (5,6), while halothane inhibits drug metabolism in vitro (7,8) and halothane, enflurane, isoflurane, and fentanyl/nitrous oxide inhibit metabolism of propranolol in dogs (1,9,10). Halothane also reduces the clearance of verapamil and fentanyl in dogs (11,12) and of lidocaine in humans (13). The effects of anesthetics on drug binding to plasma proteins are less clear: plasma protein binding of propranolol is decreased by halothane in vivo (9,14), but not in vitro (15). However, both halothane and enflurane reduce diazepam binding to human serum albumin (15).

The effects of spinal and epidural anesthesia on

drug disposition are less well defined. A decrease in hepatic blood flow produced during spinal anesthesia would be predicted to result in a decrease in the systemic clearance of drugs that have high hepatic extraction ratios and consequently exhibit flow-dependent pharmacokinetics, whereas the effects, if any, of spinal anesthesia on drug metabolism per se are uncertain. The objective of the present study, therefore, was to determine the effect of spinal anesthesia on drug disposition in the dog using propranolol as a model compound.

Methods

Approval for the study was obtained from the Vanderbilt University Division of Animal Care. Six healthy male mongrel dogs ([mean weight ± SEM] 23.3 ± 1.5 kg) were studied. Femoral artery, femoral vein, and portal vein cannulae were implanted in each dog under pentobarbital anesthesia (30 mg/kg IV) 7 days before the first study day. Arterial systemic blood pressure was measured invasively via the femoral artery cannula. Identical pharmacokinetic studies were performed in each dog on two consecutive days; on the first day, the study was performed after a single intravenous dose of thiopental (30 mg/kg); 24 hr later the study was repeated after spinal anesthesia had been established after a single intravenous dose of thiopental (30 mg/kg).

Anesthetic Protocol

On the first study day the dogs were given a dose of thiopental (30 mg/kg IV). They were then allowed to recover from anesthesia: the pharmacokinetic study was performed once consistent head raising in response to a standard auditory stimulus was observed. Twenty-four hr later, anesthesia was again induced with thiopental (30 mg/kg IV). The dogs were then placed in a prone position and flexion of the lumbar spine was achieved by inserting a 10-cm diameter cylinder under the abdomen and extending the hind legs craniad alongside the body. Using a midline approach, an 18-gauge epidural needle was introduced into the subarachnoid space at the L3–4, L4–5, or L5–6 interspace, and an epidural catheter was inserted into the subarachnoid space through the needle so that the catheter tip lay ~3–5 cm beyond the needle tip (16). Tetracaine, 1.3–1.5 mL, (10 mg/1.0 mL of 10% dextrose, i.e., 1.0% solution) was injected into the subarachnoid space when the dog was seen to consistently raise its head in response to a standard auditory stimulus.

The presence of subarachnoid anesthesia was initially determined by observing loss of tone and motor power in the hind limbs compared with the front limbs. The extent of sensory blockade was then determined at 15-min intervals by observing the response to skin pinching with nontoothed forceps (17). Supplemental doses of tetracaine (0.3–0.4 mL of 1.0% solution) were given through the catheter when diminishing levels of anesthesia were noted on two consecutive testings: five dogs required two supplemental doses, and one required three. The mean (±SEM) total dose of tetracaine administered was 20.7 ± 0.6 mg. Intravenous fluids were not given on either study day.

The pharmacokinetic study was commenced when the sensory block extended from the mid-thoracic region to the low sacral region.

Pharmacokinetic Protocol

The pharmacokinetic technique was identical on both study days. Tritiated propranolol, 200 µCi, (specific activity 67 mCi/mg, Amersham Searle Corp., Arlington Heights, IL) was injected into the femoral vein over 1 min, and simultaneously 40 mg of unlabeled propranolol was infused into the portal vein over a 10-min period by a constant infusion pump. The intraportal route was used to bypass the variable of absorption that would occur after oral administration and which might also be affected by spinal anesthesia. Arterial blood samples (4 mL) were taken 2, 4, 6, 8, 10, and 15 min after completion of the infusion, and then at 15-min intervals for the next 3.75 hr. Each blood sample was replaced by twice its volume of 0.9% saline solution. Unlabeled plasma propranolol concentrations were measured by high-pressure liquid chromatography (HPLC) and the [^{3}H]propranolol plasma concentrations were measured by liquid scintillation counting of the HPLC eluant corresponding to each propranolol peak (18).

Pharmacokinetic Calculations

Propranolol clearance (CL) after systemic (Cl_s) and portal (Cl_p) administration were calculated as:

$$Cl = dose/AUC, \qquad (1)$$

where dose is the dose of either [^{3}H]propranolol given IV or unlabeled propranolol given intraportally, and AUC is the area under the time-concentration curve

(extrapolated to infinity) calculated by the trapezoidal rule for either [^{3}H]propranolol (AUC$_{iv}$) or unlabeled propranolol (AUC$_p$). As propranolol is metabolized only in the liver and was infused into the portal vein (equivalent to 100% oral absorption), the clearance of the intraportal propranolol (Cl_p) is numerically equal to the total intrinsic clearance of propranolol (Cl_{int}) (19).

The systemic elimination rate constant (K_{el}) was calculated by linear regression analysis of the terminal phase of the time · concentration curve for [^{3}H]-propranolol, and systemic elimination half-life ($T_{\frac{1}{2}}$) was calculated as:

$$T_{\frac{1}{2}} = 0.693/K_{el}. \tag{2}$$

Volume of distribution (Vd_{SS}) was then calculated as:

$$Vd_{SS} = CL_s \cdot [AUMC/AUC], \tag{3}$$

where AUMC is the area under the moment curve. Mean hepatic plasma flow was calculated as follows: after intraportal administration of a drug of dose D_p, the amount of drug entering the systemic circulation is equal to FD_p where F is the fractional systemic availability. Thus:

$$Cl_s = F \cdot D_p/AUC_p \tag{4}$$

But

$$Cl_p = D_p/AUC_p, \tag{5}$$

Therefore

$$Cl_s = F \cdot CL_p \tag{6}$$

and

$$F = 1 - E. \tag{7}$$

Therefore

$$Cl_s = (1 - E) CL_p, \tag{8}$$

where E is the hepatic extraction ratio. Also, by the Fick principle:

$$Cl_s = Q \cdot E \tag{9}$$

where Q is the apparent hepatic plasma flow. Thus, substituting for E:

$$Q = Cl_s \cdot Cl_p/CL_p - CL_s. \tag{10}$$
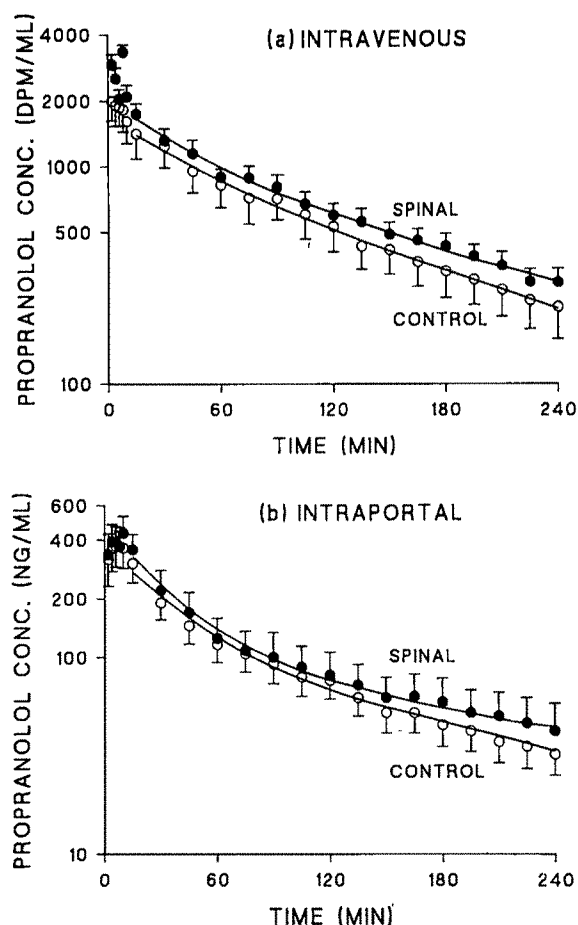
Figure 1. Plasma propranolol concentrations (mean ± SEM) after (a) femoral intravenous injection of 200 μCi of [^{3}H]propranolol and (b) the intraportal infusion of 40 mg of racemic propranolol. O, day 1, control; ●, day 2, spinal anesthesia.

Statistical Analysis

Statistical comparisons were performed using Student's t-test for paired data. $P < 0.05$ was taken as the minimum level of statistical significance. Data are expressed as mean ± SEM.

Results

Mean plasma propranolol concentrations following intraportal and intravenous administration are shown in Figure 1. There was no significant difference in the intrinsic clearance during spinal anesthesia compared with control values indicating spinal anesthesia had no effect upon liver drug metabolism (Figure 2a). Mean propranolol intrinsic clearance was 2.01 ± 0.75 L/min under control conditions on the first day, and 1.9 ± 0.7 L/min during spinal anesthesia ($P = 0.529$). Similarly, spinal anesthesia did not significantly affect either systemic clearance or hepatic plasma flow, although they were 16% and 4%
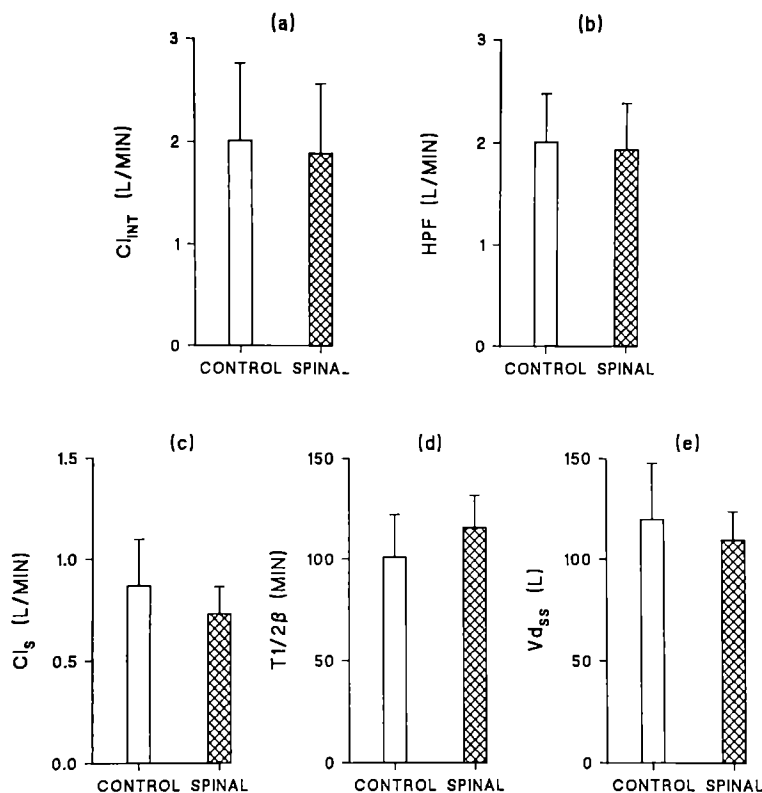
Figure 2. The lack of effect of spinal anesthesia on (a) the intrinsic clearance of propranolol, (b) mean hepatic plasma flow, (c) the systemic clearance of propranolol, (d) the elimination half life of propranolol, and (e) the volume of distribution of propranolol. Open bars, day 1, control; cross hatched bars, day 2, spinal anesthesia. Values are expressed as mean ± SEM.

lower, respectively, during the spinal anesthetic as compared to the control day (Figure 2, b and c). Mean hepatic plasma flow was 2.0 ± 0.5 L/min under control conditions and 1.9 ± 0.5 L/min during spinal anesthesia ($P = 0.832$) (Figure 2b). The lack of significant changes during spinal anesthesia in intrinsic clearance and mean hepatic plasma flow are reflected in the unchanged systemic clearance (0.9 ± 0.23 L/min control, 0.7 ± 0.13 L/min during spinal anesthesia; $P = 0.437$) and elimination half-life (101 ± 21 min control, 115 ± 16 min during spinal anesthesia; $P = 0.450$) (Figure 2, c and d). Volume of distribution (Vd_{SS}) was unchanged during spinal anesthesia (Figure 2e). Mean systolic blood pressure during the study is shown in Figure 3.

Discussion

This study shows that spinal anesthesia does not affect propranolol metabolism, in that the intrinsic clearance of propranolol, which reflects the drug metabolizing capacity of hepatic enzymes, was unchanged by spinal anesthesia. This is in contrast to other anesthetic techniques that profoundly inhibit drug metabolism. We have previously shown that the volatile (halothane, isoflurane, and enflurane) as well as intravenous anesthetics (fentanyl, propofol) re-
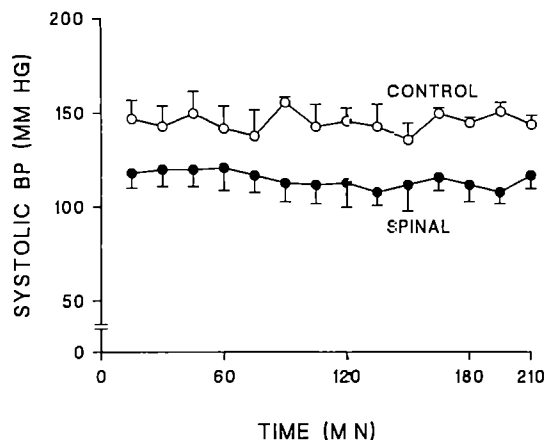
Figure 3. Systolic blood pressure (mean ± SEM) after the dual-route administration of propranolol. O, day 1, control; ●, day 2, spinal anesthesia.

duce the intrinsic clearance of propranolol under similar experimental conditions by values ranging from 40% during propofol infusion to 70% during enflurane anesthesia (1,9,10,20). Our results are in agreement with the findings of Runciman et al. (2) who showed that the hepatic extraction of cefoxitin, chlormethiazole, and meperidine were unaffected by spinal anesthesia in a chronically cannulated sheep model.

For drugs with a low hepatic extraction ratio, clearance is dependent on hepatic drug metabolizing
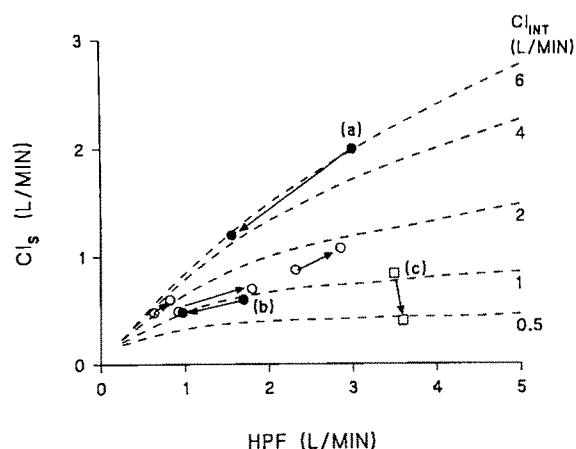
Figure 4. The relationship between hepatic plasma flow, systemic clearance, and intrinsic clearance. Dashed lines, the calculated relationship between hepatic plasma flow and systemic clearance at increasing extraction ratios on increasing values of intrinsic clearance. ●, dogs in which hepatic plasma flow fell during spinal anesthesia, but intrinsic clearance remained unchanged. Thus these dogs remained on the same intrinsic clearance curve. ○, dogs in which hepatic plasma flow increased during spinal anesthesia, but intrinsic clearance remained unchanged, again maintaining these dogs on the same intrinsic clearance curve. □, one dog in which hepatic plasma flow was unchanged by spinal anesthesia, but intrinsic clearance decreased resulting in "vertical movement" to a lower intrinsic clearance curve.

capacity, whereas the kinetics of high extraction drugs are blood flow dependent. Therefore, the relationship between hepatic plasma flow and systemic clearance depends on the intrinsic clearance in individual animals; at high intrinsic clearances this relationship is virtually linear, but at low intrinsic clearances, increases in hepatic plasma flow have little effect on systemic clearance. Our data illustrate these contrasting effects. Figure 4 shows the curves showing the calculated relationship between systemic clearance (Cl_s) and hepatic plasma flow (HPF) at varying values of intrinsic clearance (Cl_{int}). Superimposed on these calculated curves are the data from our study which illustrate the multifactorial control of drug clearance. For example, in dog a, with a high baseline intrinsic clearance, a 48% decrease in liver plasma flow produced a large (40%) decrease in systemic clearance. However, in dog b intrinsic clearance was relatively low, so that a similar proportional reduction (43%) in hepatic plasma flow only produced a 15% reduction in systemic clearance. In contrast, intrinsic clearance decreased in dog c, resulting in a decrease in systemic clearance despite hepatic plasma flow being unchanged.

Of particular interest is that Figure 4 demonstrates that during spinal anesthesia the changes in hepatic plasma flow were the primary determinant of changes in systemic clearance in all but one dog. In other words, when systemic clearance changed, it

changed on the same intrinsic clearance curve so that the dogs remained on the same curve in both studies. On the other hand, volatile anesthetics, with their profound depressant effect on drug metabolizing ability, would result in dogs moving "vertically" in Figure 4, as exemplified by dog c in Figure 4.

Spinal anesthesia did not significantly affect mean hepatic plasma flow. Several studies have investigated the effect of spinal and regional anesthesia on hepatic blood flow, in both animal models and human volunteers with conflicting results. A 23% decrease in hepatic blood flow was reported in 1970 during a study of humans undergoing spinal anesthesia (21). A decrease in hepatic blood flow was also reported in monkeys during epidural anesthesia to T-1 (22) and in dogs during high epidural blockade (23). However, studies in chronically cannulated sheep showed no significant reduction in hepatic blood flow during spinal anesthesia (2), and it has also been demonstrated in surgical patients that the addition of epidural anesthesia to halothane/nitrous oxide anesthesia does not reduce liver blood flow further than that resulting from general anesthesia alone (6). The four studies that reported reduced hepatic blood flow in response to regional anesthesia did not employ preloading with intravenous fluids prior to establishing anesthesia, whereas the two studies in which no change in hepatic blood flow was demonstrated gave intravenous fluids before induction of anesthesia. Thus it has been suggested that increasing intravascular volume is responsible for preserving cardiac output and maintaining hepatic blood flow during major regional anesthesia. However, intravenous fluids were not given in our study, (because of a possible confounding effect of such fluids on hepatic blood flow and systemic clearance), and despite this, mean hepatic plasma flow did not change.

It has been suggested that epidural anesthesia may be associated with biphasic changes in hepatic blood flow. In a study of blood volume distribution during epidural anesthesia, splanchnic blood volume initially decreased in all eight subjects (24). This was attributed to splanchnic vasoconstriction occurring in response to blood pooling in the legs. However, in two subjects a secondary increase in splanchnic blood volume occurred, resulting in marked systemic hypotension. The method of estimating mean hepatic plasma flow used in our study measures an integrated value for hepatic plasma flow over the 4-hr study period, so that transient changes in opposite direction might be negated.

We conclude, therefore, that spinal anesthesia has no effect on drug metabolism in the liver. In addition,

although a consistent change in hepatic plasma flow during spinal anesthesia did not occur, we have demonstrated that changes in drug disposition that do occur during spinal anesthesia are almost exclusively mediated by changes in hepatic plasma flow. Thus, the disposition of drugs administered intravenously during spinal anesthesia will be dependent primarily upon the sensitivity of these drugs to changes in hepatic blood flow; the effect of changes in hepatic blood flow on drug disposition will be most marked for drugs with high hepatic extraction ratios and negligible for drugs with low extraction ratios.

References

1. Reilly CS, Wood AJJ, Koshakji R, Wood M. Effect of enflurane anaesthesia on drug disposition in the dog. Br J Anaesth 1986;58:802P.

2. Runciman WB, Mather LE, Ilsley AH, Carapetis RJ, Upton RN. A sheep preparation for studying interactions between blood flow and drug disposition: III. Effects of general and spinal anaesthesia on regional blood flow and oxygen tensions. Br J Anaesth 1984;56:1247–57.

3. Thomson IA, Hughes RL, Fitch W, Campbell D. Effects of nitrous oxide on liver haemodynamics and oxygen consumption in the greyhound. Anaesthesia 1982;37:548–53.

4. Hughes RL, Campbell D, Fitch W. Effects of enflurane and halothane on liver blood flow and oxygen consumption in the greyhound. Br J Anaesth 1980;52:1079–86.

5. Gelman SI. Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 1976;111:881–3.

6. Nancarrow C, Plummer JL, Ilsley AH, McLean CF, Cousins MJ. Effects of combined extradural blockade and general anaesthesia on indocyanine green clearance and halothane metabolism. Br J Anaesth 1986;58:29–36.

7. Brown BR. The diphasic action of halothane on the oxidative metabolism of drugs by the liver: an in vitro study in the rat. Anesthesiology 1971;35:241–6.

8. Brown BR. Effects of inhalation anesthetics on hepatic glucuronide conjugation: a study of the rat in vitro. Anesthesiology 1972;37:483–8.

9. Reilly CS, Wood AJJ, Koshakji RP, Wood M. The effect of halothane on drug disposition: contribution of changes in intrinsic drug metabolizing capacity and hepatic blood flow. Anesthesiology 1985;63:70–6.

10. Reilly CS, Merrell J, Wood AJJ, Koshakji RP, Wood M. Comparison of the effects of isoflurane or fentanyl-nitrous oxide anaesthesia on propranolol disposition in dogs. Br J Anaesth 1988;60:791–6.

11. Chelly JE, Hysing ES, Abernethy DR, Coursou MF, Merin RG. Effects of inhalational anesthetics on verapamil pharmacokinetics in dogs. Anesthesiology 1986;65:266–71.

12. Borel JD, Bentley JB, Nenad RE, Gillespie RE. The influence of halothane on fentanyl pharmacokinetics (abstract). Anesthesiology 1982;57:A239.

13. Bentley JB, Glass S, Gandolfi AJ. The influence of halothane on lidocaine pharmacokinetics on man (abstract). Anesthesiology 1983;59:A246.

14. Gordon L, Wood AJJ, Koshakji RP, Wilkinson GR, Dupont WD, Wood M. Acute effects of halothane anesthesia on arterial and venous concentrations of propranolol in the dog. Anesthesiology 1987;67:225–30.

15. Dale O, Nilsen OG. Displacement of some basic drugs from human serum proteins by enflurane, halothane and their major metabolites: an in vitro study. Br J Anaesth 1984;56:535–41.

16. Feldman HS, Covino BG. A chronic model for investigation of experimental spinal anesthesia in the dog. Anesthesiology 1981;54:148–52.

17. Lebeaux MI. Experimental epidural anaesthesia in the dog with lignocaine and bupivacaine. Br J Anaesth 1973;45:549–55.

18. Koshakji RP, Wood AJJ. A modified sensitive liquid chromatographic method for measurement of propranolol with fluorescence detection. J Pharm Sci 1986;75:87–9.

19. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 1975;18:377–90.

20. Perry SM, Whelan E, Shay S, Wood AJ, Wood M. Effects of propofol on drug disposition: marked effects on drug distribution, less effect on drug metabolism (abstract). Anesthesiology 1988;69:A461.

21. Kennedy WF, Everett GB, Cobb LA, Allen GD. Simultaneous systemic and hepatic hemodynamic measurements during high spinal anesthesia in normal man. Anesth Analg 1970;6:1016–24.

22. Sivarajan M, Amory DW, Lindbloom LE. Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey. Anesthesiology 1976;45:300–10.

23. Greitz T, Andreen M, Irestedt L. Haemodynamics and oxygen consumption in the dog during high epidural block with special reference to the splanchnic region. Acta Anaesthesiol Scand 1983;27:211–7.

24. Arndt JD, Hock A, Stanton-Hicks M, Stuhmeier KD. Peridural anesthesia and the distribution of blood in supine humans. Anesthesiology 1985;63:616–23.

Effect of N₂O on Segmental Left Ventricular Function and Effective Arterial Elastance in Pigs When Added to a Halothane-Fentanyl-Pancuronium Anesthetic Technique

André Coetzee, FFA(SA), MMed, FFARCS, PhD, MD, Pieter Fourie, BSc, MB, ChB, PhD,
Chris Bolliger, MD, Emmerentia Badenhorst, NDT, Aart Rebel, BSc, and Carl Lombard, PhD

COETZEE A, FOURIE P, BOLLIGER C, BADENHORST E, REBEL A, LOMBARD C. Effect of N₂O on segmental left ventricular function and effective arterial elastance in pigs when added to a halothane-fentanyl-pancuronium anesthetic technique. Anesth Analg 1989;69:313–22.

The interaction of various concentrations of N₂O and a stable halothane-fentanyl-pancuronium anesthetic technique was examined in nine pigs. Segmental myocardial contractility was measured with the end-systolic pressure-length relationship (E_{es}), and the effective arterial elastance (E_a) was quantified based on the Windkessel model. The addition of 30, 50, and 70% N₂O did not change myocardial contractility or the effective arterial elastance. During the 30 and 70% N₂O challenge, however, arterial capaci-

tance decreased significantly from a mean (± SEM) 0.86 ± 0.15 to 0.71 ± 0.0.11 mL/mm Hg with 30% N₂O ($P < 0.05$) and from 0.90 ± 0.09 to 0.71 ± 0.07 mL/mm Hg ($P < 0.05$) with 70% N₂O. A dose-response relationship for the effect on the arterial capacitance could not be demonstrated. We concluded that in the presence of halothane, fentanyl, and pancuronium, N₂O does not depress the normal myocardium or change left ventricular afterload. The decrease in arterial capacitance that occurred when 30 and 70% N₂O were given was not sufficient to change the effective afterload and appears to be of no importance to normal left ventricular function.

Key Words: ANESTHETICS, GASES—nitrous oxide. HEART, END-SYSTOLIC PRESSURE-LENGTH RELATIONSHIP.

The cardiovascular effects of N₂O have been evaluated in many previous studies (1–12). However, the problems with quantifying myocardial contractility and left ventricular afterload make it difficult to draw conclusions from some of these studies. For example, regional myocardial shortening is a volume-based index of myocardial function and afterload interaction and does not necessarily reflect myocardial contractility (11).

Because N₂O is not used as a single drug in general anesthesia, we thought it would be informative to evaluate the effect of N₂O in the presence of other commonly used anesthetic agents. A balanced anes-

thetic technique combining a potent inhalation anesthetic agent with a short-acting analgesic and a muscle relaxant is very common, and this study was, therefore, devised to answer the following questions:

1. Does N₂O depress left ventricular (segmental) myocardial contractility as measured by segmental maximal time-varying elastance (E_{es})?
2. Does N₂O change the arterial afterload (E_a)?

These questions were studied in pigs with a normal heart anesthetized with halothane and fentanyl after induction of anesthesia with thiopental.

Methods

This study was approved by the Ethical Committee of the Faculty of Medicine, University of Stellenbosch. The animals were cared for in accordance with University and national guidelines.

Nine pigs (mean weight 25 kg) were studied. The morning of surgery, an intravenous infusion was

started, thiopental (2 mg/kg) and fentanyl (20 μg/kg) were given intravenously, and a tracheostomy was performed. The trachea was intubated and the lungs ventilated with 60% nitrogen and 40% oxygen, using a fresh gas flow of 3 L/min by means of a circle system equipped with a CO_2 absorber. The inspired oxygen concentration was measured with a calibrated oximeter (Servo Gas Monitor, Siemens, West Germany). Tidal volume and ventilation frequency were adjusted to maintain the $PaCo_2$ between 35 and 37 mm Hg. Halothane (0.5%) was administered throughout the experiment from a calibrated vaporizer (Drägerwerk, West Germany), and the end-expired halothane concentration was constantly monitored (Servo Gas Monitor, Siemens). Fentanyl was infused at a rate of 10 μg·kg^{-1}·hr^{-1}. The animals were paralyzed with an initial dose of pancuronium (0.1 mg/kg), and thereafter, paralysis was maintained with an infusion of 0.15 mg·kg^{-1}·hr^{-1}.

Temperature of the animals was monitored using the thermistor of a pulmonary artery catheter, and was kept between 36.7 and 37.2°C with a below-table heating system. Normal saline solution was infused at a rate of 5 mL·kg^{-1}·hr^{-1}.

A cannula was inserted through a lateral neck incision through the carotid artery into the aorta until the tip of the catheter was within 1 cm of the aortic valve. Systemic blood pressure and the aortic pressure at the end of systole (P_{es}; the pressure at the incisura on the aortic pressure recording) were recorded with transducers (Statham P23, Statham; natural frequency 50.3 Hz). The natural frequency for the total recording system (cannula, conduction lines, transducers, and recording apparatus) was 26.8 Hz.

A pulmonary artery catheter (Edwards Laboratories, Puerto Ricco) was inserted into the pulmonary artery through the external jugular vein. The position of the catheter was verified after the chest had been opened, and the injection port was demonstrated to be in the right atrium after completion of the experiment. Cardiac output was measured by thermodilution (Mansfield 9530, Mansfield, MA) after manual injection of 5 mL of dextrose at 0°C into the proximal port. Injections were started at the end of expiration and each was completed in <4 sec. The mean of three values is reported in this study and the coefficient of variation for the 54 triplicate determinations was 5.2%.

Both femoral arteries were exposed. A microtip flow catheter (Miller Instruments, Houston, TX) was advanced through one artery until the tip of the catheter was just distal to the aortic valve. The position of this catheter was also verified once the chest was opened, as well as during postmortem
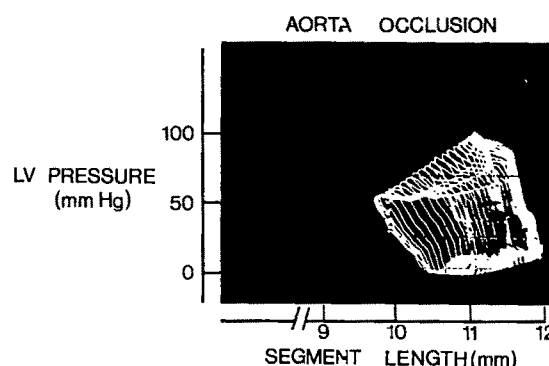
AORTA   OCCLUSION

Figure 1. Various pressure-length loops obtained by partial occlusion of the aorta with an intraaortic balloon. Note the linear character of the various end-systolic pressure and length points (ESPL). The slope of the line connecting the end-systolic pressure-length points is an index of myocardial contractility (maximal time varying elastance or E_{es}). LV = left ventricular.

dissection. Because the area under the velocity signal is equal to the delivered stroke volume (which was obtained from cardiac output and heart rate recordings), the velocity signal could be recalibrated for blood flow and blood acceleration.

Through the opposite femoral artery, an occlusion balloon catheter (Edwards Laboratories; size 8/14 F) was positioned in the descending aorta. The balloon was only used to momentarily vary ventricular afterload to obtain various pressure-length loops for the left ventricle (Figure 1) (13).

A thoracotomy and pericardectomy were performed, and the heart suspended in a pericardial cradle without obstructing the venous inflow to the heart. A 16-gauge cannula was sutured into the apex of the left ventricle, and intraventricular pressure was recorded with a transducer (Statham P23Db, natural frequency 50.6 Hz). In addition, the pressure was amplified to obtain left ventricular end-diastolic pressure. From the left ventricular pressure signal, a computer-calculated heart rate was obtained.

Two piezoelectric crystals were inserted 1-cm apart into the left ventricular subendocardium, perpendicular to and midway between the apex and base axis of the heart, and 1–1.5 cm from the left anterior descending coronary artery. These crystals were used to measure segmental length during the cardiac cycle. The transit time of an ultrasound beam between the two crystals was recorded (Ultrasonic Dimension System, Schuessler and Associates Cardiff-by-the Sea, CA). Because the velocity of ultrasound in the myocardium is constant (1.56 mm/μsec), the instantaneous distance between the pair of crystals could be calculated (14). The maximal segmental length (L_{max}) was taken at the point where the sharp upslope of the left ventricular pressure began, and the minimal length (L_{min}) was taken at the time the aortic valve

closed. Systolic shortening (dL) could then be determined (dL = $L_{max} - L_{min}$). The difference in dL was normalized for L_{max} and expressed as a percent (dL%).

Combined left ventricular pressure and segmental length changes were displayed on a storage oscilloscope (Tektronix Inc., model 5103 N, Guernsey, Channel Islands) to give a beat by beat recording of left ventricular pressure-length loop (P-L loop) (15).

Arterial blood gas tensions, pH, HCO_3^- and hemoglobin concentration were measured with an automated pH and blood gas analyzer (Corning, model 168, Medfield, MA).

Calibration of the pressure transducers (using a mercury manometer) was performed before commencing the experiments, as well as between each step of the experiments. Signals were recorded on paper (Beckman, Palo Alto, CA) 15 sec after the tracheostomy tube was disconnected from the ventilator, and were digitized (ADA converter, SED, University of Stellenbosch Tygerberg, South Africa). A microcomputer (Olivetti, model M24, 640 KB with 8087 mathematical microprocessor) stored data directly on floppy diskette. Data sampling was done at 200 Hz for 5 sec, which allowed for the registration of a number of cardiac cycles.

Experimental Protocol

After surgery was completed, 45 min were allowed for the animal to stabilize before the experiment continued. The animals' lungs were ventilated with the following gas concentrations:

30% O_2 + 70% N_2, followed by 30% O_2 + 70% N_2O
50% O_2 + 50% N_2, followed by 50% O_2 + 50% N_2O
70% O_2 + 30% N_2, followed by 70% O_2 + 30% N_2O

The N_2-oxygen mixture was always followed by an equivalent N_2O-oxygen mixture (i.e., only the N_2 was changed for N_2O). The inspired concentration of N_2 and N_2O was not directly measured, but the oximeter reading was kept constant for the particular concentration of O_2, when N_2 was changed to N_2O. Twenty-five minutes were allowed for stabilization with each new gas mixture before measurements were recorded. The O_2, N_2, and N_2O concentrations were varied at random in each animal according to a Latin square design to avoid artifacts that could be due to differences in the time from the start of the experiment (16). Three replicates of the Latin square layout were used to give a total of nine pigs. However, as indicated, specific concentrations of N_2 and N_2O were kept together to allow for a comparison between

values obtained with and without N_2O for a particular O_2 concentration.

The various end-systolic pressure-length points used to construct the E_{es} were obtained by inflating the balloon in the aorta over a 5-sec period while the pressure-length loops were recorded (Figure 1). The computer identified the maximal pressure-length ratio for the control study and each of the subsequent afterloaded contractions, and constructed the end-systolic pressure-length line (E_{es}).

Hemodynamic data were recorded before the balloon was inflated to avoid residual effects on the general hemodynamics, which could have been introduced by the increase in afterload.

Three additional pigs were subjected to a similar general anesthetic technique and surgery without the challenge of N_2O. Cardiovascular parameters were measured after the completion of surgery and after 150 min to evaluate the effect of time on the model.

Calculations

Mean arterial pressure was calculated by computer, with reference to the area under the aorta pressure curve.

Calculations of changes in segmental left ventricular elastance with time are based on pressure-length loops that describe a single cardiac cycle in terms of pressure and segmental length (17,18). From the pressure-length loops obtained by varying the afterload with the aortic balloon, the computer identified the maximal pressure-length ratio for each contraction (Figure 1). Regression analysis was then performed on these points, and the slope of this analysis was termed the maximal time-varying elastance (E_{es}) (in mm Hg/mm) and was used as an index of segmental myocardial contractility (17,18). The intercept on the length axis (i.e., the segmental length of the left ventricular minor axis when the ventricular pressure is zero) is indicated with the symbol L_o and has units of mm.

The hydraulic impedance (Z) of the aorta was modeled by the Windkessel model (Appendix A) (19,20). The effective arterial elastance (E_a) is the slope of the arterial end-systolic pressure-stroke volume relationship. This is a lumped characterization of the arterial impedance and incorporates the influence of heart rate in terms of duration of ejection (ts) and arterial diastole (td).

E_a is calculated from the equation:

$$E_a = (Ro + Rp)/[ts + \tau(1 - exp^{-td/\tau})],$$

where τ is the time constant of the diastolic pressure wave and E_a has units of mm Hg/cc (20).

Table 1. Effect of 30%, 50%, and 70% N_2O on the Cardiovascular Parameters in the Normal Pig

	HR (b/min)	MAP (mm Hg)	SV (mL)	CO (L/min)	LVEDP (mm Hg)	Lmax (mm)	Lmin (mm)	dL (mm)
30% Nitrogen	121.84	88.34	24.82	3.02	8.59	13.03	10.66	2.38
	±4.46	±6.87	±1.83	±0.24	±0.85	±0.64	±0.60	±0.19
30% Nitrous oxide	129.46	94.10	23.69	3.04	9.59	12.97	10.71	2.25
	±4.45	±7.29	±2.15	±0.28	±0.94	±0.70	±0.63	±0.14
50% Nitrogen	120.29	89.26	25.28	3.03	8.44	12.99	10.60	2.40
	±19.20	±5.14	±2.40	±0.32	±0.76	±0.75	±0.65	±0.18
50% Nitrous oxide	123.68	91.12	26.71	3.27	9.67*	13.19	10.73	2.47
	±7.34	±8.29	±2.28	±0.28	±0.86	±0.74	±0.66	±0.20
70% Nitrogen	124.37	86.10	26.04	3.21	9.28	12.90	10.67	2.23
	±6.42	±6.86	±2.22	±0.29	±0.96	±0.68	±0.64	±0.21
70% Nitrous oxide	127.30	94.69*	24.70	3.06	10.22	13.06	10.78	2.28
	±7.10	±6.60	±2.35	±0.27	±0.83	±0.68	±0.64	±0.18

Values are the mean ± SEM for 9 animals. Ro and Rp are the resistive components of the arterial system, and C is the capacitance. P_{es} = LV end-systolic pressure; E_{es} = end-systolic pressure-length relationship; L_0 = LV segment length when LV pressure is zero; dL = segmental shortening during systole; dL/L_{max} = segmental shortening normalized to maximum segment length. These are used in the calculation of the effective arterial elastance (E_a) as described in Appendix A. Statistically significant differences between equivalent concentrations of N_2 and N_2O are indicated with an asterix.
* $P < 0.05$
† $P < 0.01$

Global left ventricular stroke work was calculated as (mean arterial pressure stroke volume).

Statistical Analysis

In the Latin square layout used, the experimental factors of interest were the mixture concentration effect, the period effect, and the carryover effects.

For each variable, the value obtained in the preceding O_2/N_2 period was subtracted from the measurement of that variable obtained in the corresponding O_2/N_2O period. These differences were used in the design analyses.

Multivariate analysis of variance and multivariate-rank tests were applied to test for a significant overall N_2O effect. Analysis of variance was used to test for significant differences between mixture concentration levels and for significant carryover effects. To determine the N_2O concentration at which effects occurred, univariate tests were conducted at each concentration level. A significance level of 0.05 was used in all the analyses.

Regression analysis utilized the method of least squares. Pearson correlation coefficient was used to demonstrate correlations.

Results

All values reported are the mean ± SEM for nine experiments. Results from various parameters are indicated in Tables 1 and 2.

Results Pertaining to the Model

1. *The end-systolic pressure-length relationship; segmental and global LV work.* The mean number of points used to construct an end-systolic pressure-length line was 7.93 (range 5–11). The correlation coefficient for the 54 end-systolic pressure-length lines constructed in the course of the experiment range from 0.992 to 0.996, with a mean value of 0.994. In Figure 2, six randomly selected lines are presented to demonstrate the small scatter of the pressure-length points around the regression line.

2. *Stability of the model.* To evaluate the effect of time on cardiovascular mechanics, three pigs were subjected to the anesthetic and surgical protocol as indicated in the Method section. Animals were left undisturbed for 2.5 hr, and cardiovascular parameters were recorded after completion of surgery and at the end of the 150-min period (Table 3). Because of the small sample number, statistical analysis was not attempted.

Effect of N_2O

Myocardial contractility, indicated by E_{es}, remained constant and the extrapolated segment length at the time left ventricular pressure was zero (L_0) did not change. There was, therefore, no change in contractility or a parallel shift in the systolic pressure-length relationship of the left ventricle (Figure 3).

The effective arterial elastance (E_e) did not change significantly after the N_2O challenge. Univariate analysis demonstrated a significant difference for mean arterial pressure between 70% N_2 and 70% N_2O.

Table 1. *Continued*

	dL/L$_{max}$ (%)	Rp (mm Hg·sec^{-1}·mL^{-1})	R$_o$	C (mL/mm Hg)	E$_a$ (mm Hg/mL)	P$_{es}$ (mm Hg)	E$_{es}$ (mm Hg/mm)	L$_o$ (mm)
30% Nitrogen	18.38	1.71	0.15	0.86	4.08	94.90	53.33	8.24
	±1.45	±0.21	±0.04	±0.15	±0.52	±6.13	±14.58	±0.90
30% Nitrous oxide	17.54	2.02	0.07	0.71*	4.48	101.00	49.83	8.48
	±1.06	±0.29	±0.02	±0.11	±0.30	±6.96	±6.13	±0.94
50% Nitrogen	18.57	1.90	0.11	0.86	4.03	90.60	66.70	8.64
	±1.09	±0.35	±0.02	±0.10	±0.39	±5.45	±18.94	±1.07
50% Nitrous oxide	18.88	1.75	0.08	0.77	4.07	97.47	49.18	8.24
	±1.35	±0.26	±0.02	±0.08	±0.68	±6.66	±10.11	±1.00
70% Nitrogen	17.46	1.86	0.12	0.90	3.97	88.51	57.62	8.84
	±1.61	±0.43	±0.03	±0.09	±0.56	±4.44	±10.61	±0.91
70% Nitrous oxide	17.65	1.90	0.10	0.71*	4.16	97.40†	47.30	8.45
	±1.38	±0.34	±0.02	±0.07	±0.42	±4.86	±7.68	±1.01

Use of MANOVA showed a significant decrease in the arterial compliance after the introduction of N$_2$O into the anesthetic breathing circuit. Univariate analysis indicated a difference for arterial compliance at the 30% N$_2$O and 70% N$_2$O concentrations.

Left ventricular end-diastolic pressure increased when N$_2$O replaced N$_2$ (MANOVA). Univariate analysis could only confirm an increase when 50% N$_2$O replaced 50% N$_2$.

Multivariate analysis indicated a difference for P$_{es}$ that tested significantly different for 70% N$_2$O/O$_2$ compared with 70% N$_2$/O$_2$.

Discussion

Because of the other drugs employed, this study should not be regarded as a pharmacologic study of the effect N$_2$O on the heart and circulation. Because the combination of halothane, fentanyl, and pancuronium is often used, we attempted to evaluate the effect of N$_2$O on the circulation in the presence of these drugs. However, because halothane, fentanyl, and pancuronium were administered in a controlled fashion and comparisons were made between results obtained in the presence and absence of N$_2$O, we assumed that change, if present, was caused by the addition of N$_2$O, and accepted that changes reflect an interaction between N$_2$O and the other drugs, rather than an effect of N$_2$O alone.

Results from our study indicate that the addition of 30, 50, and 70% N$_2$O to stable halothane-fentanyl-pancuronium anesthesia does not affect myocardial contractility and is not associated with a parallel shift in the pressure-length relations (L$_0$ remained constant). Previous studies (1–12) have indicated various effects of N$_2$O on the heart, although the experimental designs, measurement techniques, and drugs employed were not similar to our study. It is, however, relevant to note that some experiments (1–3) in isolated heart muscle and intact animals demonstrated myocardial depression when the hearts were exposed to N$_2$O. To complicate the interpretation from the isolated heart studies further, another study (4) has indicated that both N$_2$O and N$_2$ were associated with myocardial depression. The authors concluded that the effects were due to hypoxia, rather than a specific effect of N$_2$O or N$_2$.

A study (6) of healthy volunteers demonstrated myocardial depression when subjects received 40% N$_2$O. However, in those experiments, the systemic vascular resistance also increased, and this may have affected the index of contractility used (ballistocardiography) without myocardial contractility actually having changed. More recently, results from studies (11) in dogs suggested that provided coronary blood flow is normal, N$_2$O does not affect segmental myocardial function as measured by systolic shortening.

Our results support some of those from previous reports, but contradict others. Conclusive comparisons are not possible because of numerous differences in experimental design. Therefore, we can only discuss possible drug interactions in our study with reference to the previous studies.

We used thiopental to induce anesthesia, and a previous study (21) has shown that thiopental blood concentrations of 60–100 μg/mL are associated with myocardial depression. We did not measure thiopental blood levels in this study, but have observed a low and constant blood concentration of thiopental in dogs after using 15 mg/kg for induction of anesthesia (13). Although it is inappropriate to extrapolate directly, we think that the previous experiments place some perspective on the possible role played by thiopental. Note that in the present study, the dose of thio-

Table 2. Minimum and Maximum Values Obtained for Certain Cardiovascular Parameters[a]

Experiment	HR b/min min	HR b/min max	MAP (mm Hg) min	MAP (mm Hg) max	SV (mL) min	SV (mL) max	dL/L_{max} (%) min	dL/L_{max} (%) max	E_{es} (mm Hg/mm) min	E_{es} (mm Hg/mm) max	E_a (mm Hg/mL) min	E_a (mm Hg/mL) max
1	142	152	93	109	22	29	16	21	33	41	3.5	4.8
2	108	139	77	89	24	32	22	28	30	53	2.0	3.3
3	114	121	60	83	32	31	13	16	60	65	4.3	6.2
4	114	118	64	92	20	23	18	22	20	40	2.3	3.6
5	115	153	74	127	12	15	13	16	41	79	3.5	6.8
6	103	112	109	145	32	40	19	21	22	54	3.5	6.7
7	106	108	65	69	21	27	16	18	33	44	2.4	3.3
8	111	129	86	101	24	28	18	23	27	54	2.7	3.4
9	141	150	80	95	27	31	16	17	52	73	2.2	3.5

[a] Range includes the N_2 and various N_2O concentrations.

pental was much less than that used in our previous study (13).

The interaction between N_2O and halothane has been examined extensively. In dogs, the combination of halothane and N_2O results in cardiac depression (measured by aortic blood acceleration) greater than that observed with either drug alone (2). In healthy patients, the addition of N_2O to halothane was associated with less cardiovascular depression than when halothane alone was used (8). That particular study (8) and another clinical study (7) indicated that N_2O is associated with an increase in circulatory levels of norepinephrine, but this could not be confirmed in a more recent publication (10).

The interactions between N_2O and fentanyl involving the cardiovascular system have been examined in dogs. In the in vitro canine papillary muscle preparation, the combination of N_2O and fentanyl has an additive depressant effect on myocardial contractility (22). However, in the intact animal, no interaction was observed (11).

Except for methodologic differences between our study and previous studies, one of our concerns centers on possible artifacts introduced by measurement techniques of myocardial contractility that are not independent of the loading conditions of the heart. Ballistocardiography (23), dP/dt_{max}, blood acceleration, and systolic fiber shortening are affected by both preload and afterload (24,25). To overcome this particular problem, we elected to test the effect of N_2O in a clinically relevant setting, using the end-systolic pressure-*length* relationship (E_{es}). The end-systolic pressure-*volume* relationship is a load-independent measurement of global myocardial contractility (26–28) and is relatively insensitive to changes in heart rate (29,30). Although the end-systolic pressure-*length* relationship is used to quantify regional myocardial contractility, the relationship

between global and segmental myocardial function is well established (15). We previously demonstrated the ability of the regional E_{es} to reflect changes in myocardial contractility induced by inhalation anesthetic agents (13) and, furthermore, that this index is load-independent (31).

Because of the known inverse interaction between stroke volume and afterload (32), changes in afterload will affect cardiac output in the presence of myocardial contractility proven to be stable during the N_2O challenges. We choose to define afterload as "external factors which oppose shortening of the heart muscle" (33,34), and our results indicate that left ventricular afterload did not change during the administration of N_2O. However, when the various components of the effective arterial elastance (E_a) were examined, vascular compliance decreased when 30 and 70% N_2O were added to the already existing anesthetic technique.

Halothane alone does not change arterial impedance (35), nor does the combination of fentanyl and N_2O in patients with good left ventricular function change systemic vascular resistance (36). Previous results (37) indicate that pancuronium causes an atropine-like effect and an increase in blood pressure. Again, however, differences in experimental design make it impossible to determine whether N_2O does or does not have any specific cardiovascular interaction with pancuronium under the conditions of the present study (38, 39).

As far as animal experiments can be extrapolated to human patients, the present results indicate that the circulation is not adversely affected when N_2O is added to a halothane-pancuronium-fentanyl anesthetic technique. It should also be kept in mind that this study was done in pigs with a normal heart and does not indicate what the effect might be in the presence of a diseased heart.
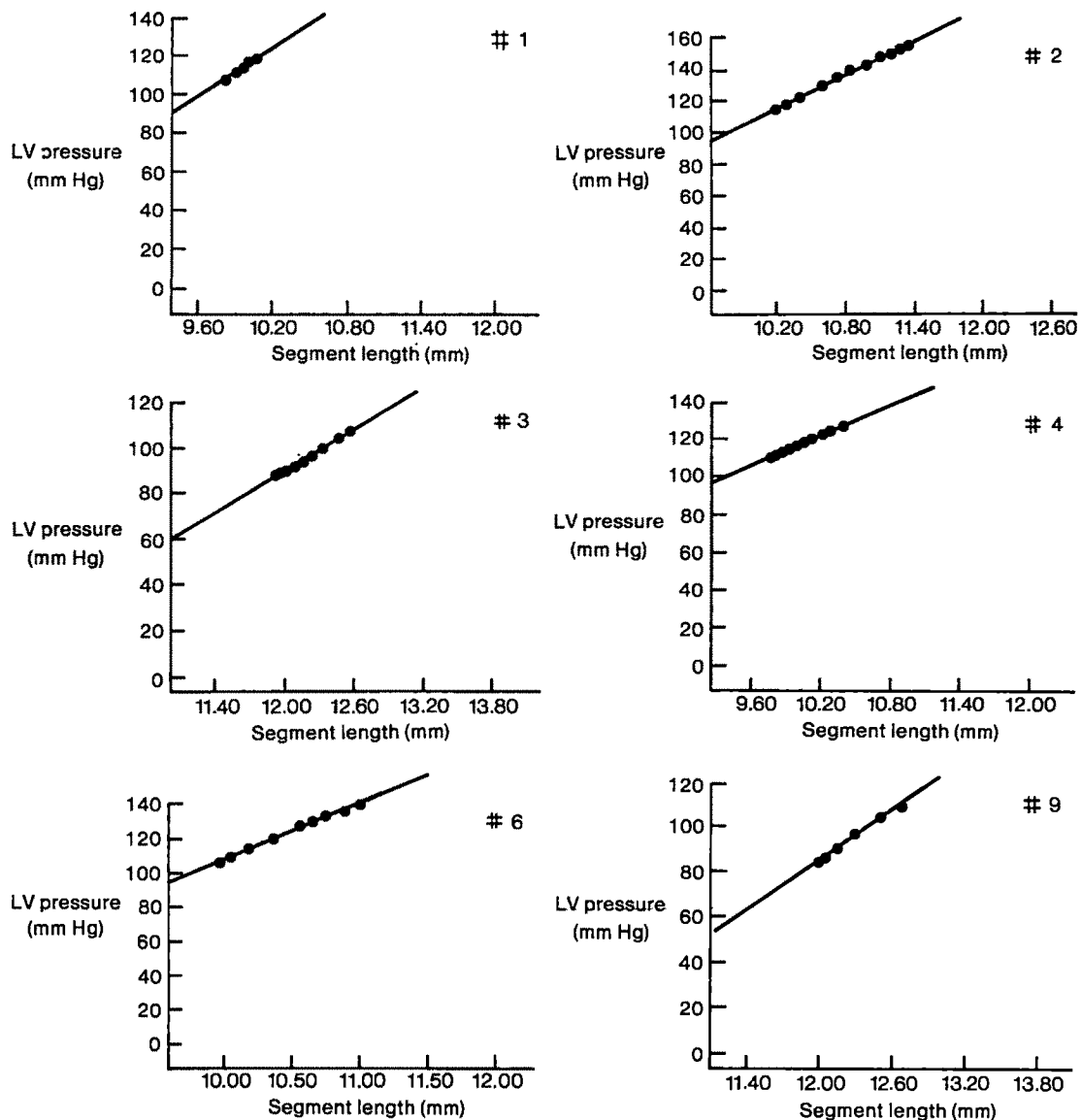
Figure 2. Six randomly selected end-systolic pressure-length loops (from a total of 54) demonstrate the small scatter of the points around the end-systolic pressure-length loop obtained by regression analysis. LV = left ventricular.

Appendix A

The components of the Windkessel model can be related to the properties of the arterial bed (40). Theoretically, the input impedance, $Z(\omega)$, of the aorta can be calculated from the equation:

$$Z(\omega) = (Ro + Rp)/1 + j\omega RpC \qquad (1),$$

where ω is equal to $2f$, f the frequency component, and j = phase difference of 90°. Ro and Rp are the resistive properties of the arterial system, and C is the capacitance (Figure 4) (40,41).

The input impedance has a maximal value at zero frequency (Figure 4) and, hence,

$$Z(o) = Ro + Rp \qquad \text{for } f = 0$$
$$= MAP/MF$$
$$= Rin \qquad (2),$$

where MAP = mean arterial pressure, MF = mean flow, and Rin = input resistance when $f = 0$ (Figure 4) (42).

From Equation 2, Rp can be calculated:

$$Rp = Rin = MAP/MF - Ro \qquad (3).$$

(Note that the downstream pressure of the input

Table 3. Cardiovascular Parameters to Illustrate the Influence of Time on the Animal Model

Time (min)	HR (b/min)	MAP (mm Hg)	SV (mL)	CO (L/min)	LVEDP (mm Hg)	E_{es} (mm Hg/mm)	E_a (mm Hg/mL)	L_o (mm)	L_{max} (mm)	dL (mm)	dL/L_{max} (%)
0	95.90	79.77	32.57	3.01	16.67	67.17	3.72	8.38	11.97	2.13	17.31
150	100.20	80.27	31.23	3.03	16.00	68.20	3.93	7.71	11.30	2.08	17.75

Values are the mean for 3 experiments. Statistical analysis was not attempted because of the small sample.
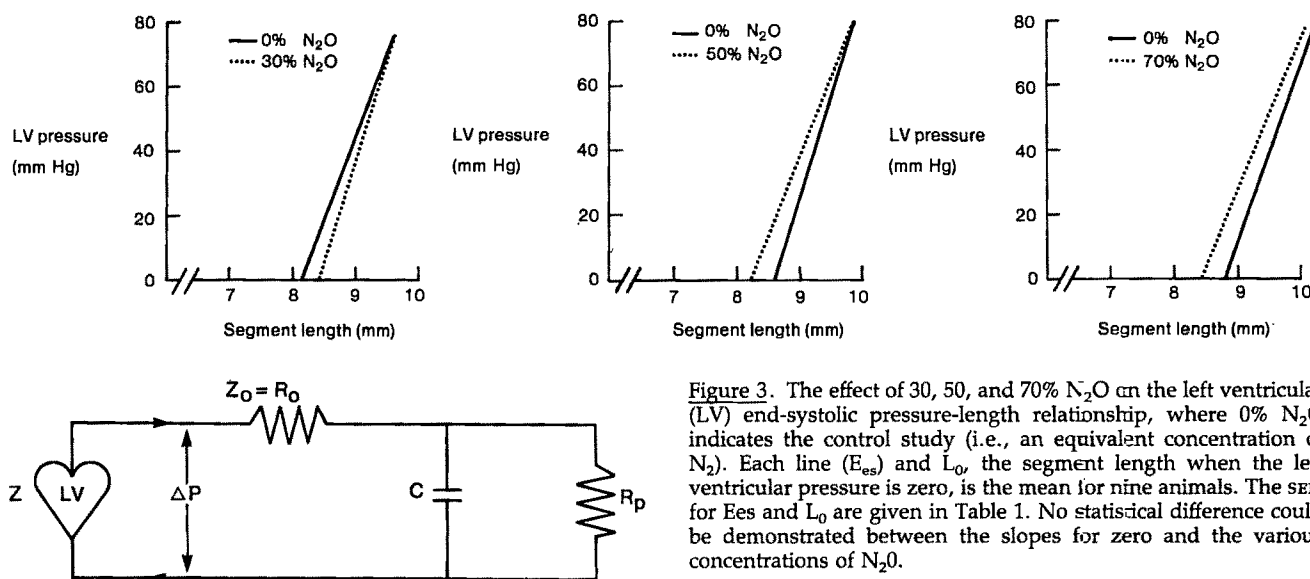
Figure 3. The effect of 30, 50, and 70% N_2O on the left ventricular (LV) end-systolic pressure-length relationship, where 0% N_2O indicates the control study (i.e., an equivalent concentration of N_2). Each line (E_{es}) and L_o, the segment length when the left ventricular pressure is zero, is the mean for nine animals. The SEM for Ees and L_0 are given in Table 1. No statistical difference could be demonstrated between the slopes for zero and the various concentrations of N_2O.

Figure 4. Diagram of the Windkessel model. The left ventricular (LV) experiences an impedance (Z), which is a combination of the characteristic impedance (Z_0) that is mainly resistive (hence $Z_0 = R_0$), the peripheral resistance (R_p), and a capacitance (C).

resistance is not subtracted from the mean arterial pressure in terms of the applied definition [43].)

Because waves are partially reflected at the bifurcation of the arterial network, this must be considered in the calculation of impedance:

$$Z = Zo (1 + \delta)/(1 - \delta) \qquad (4)$$

where δ is the reflection coefficient, Z is the input impedance, and Zo is the characteristic impedance of the tube (44). In the absence of reflections (i.e., $\delta = 0$), the input impedance approximates the characteristic impedance. This especially applies at the higher frequencies when, during the rapid inflow of blood into the aorta at the beginning of systole, the increase in pressure and blood flow has a linear character, which signifies an ohmic resistance (zero-phase difference between pressure and flow) (45). Therefore,

$$Zo = Ro = dP/dQ \qquad (5)$$

The effective capacitance of the arterial system can be calculated from the diastolic pressure wave, as-

suming a monoexponential decay (46). The time constant is determined from:

$$\tau = RpC = td/(\ln P_{es} - \ln DAP) \qquad (6)$$

where td is the diastolic time interval, P_{es} is the end systolic pressure, and DAP the diastolic arterial pressure.

The effective arterial elastance (E_a) represents the arterial impedance (with certain simplifying assumptions) and incorporates the heart rate (47).

$$Ea = (Ro + Rp)/(ts - \tau[1 - exp^{-td/\tau}]) \qquad (7)$$

The value for E_a can also be calculated from the ratio of the end-systolic pressure to the stroke volume (Pes/SV) (47). To verify the application of the Windkessel calculations as used in our studies, we normalized the calculated E_a (mm Hg/mL) to have similar units as the pressure-length relations utilized in this study by multiplying E_a with a factor (SV/dL), where SV = stroke volume and dL = segmental systolic shortening. When a separate correlation coefficient was calculated for the data of each animal, r values ranged from 0.71 to 0.98. The mean r was 0.92 (SEM = 0.091).

References

1. Price HL. Myocardial depression by nitrous oxide and its reversal by Ca^{2+}. Anesthesiology 1976;44:211–5.

2. Eisele JH, Trenchand D, Stubbs J, Guz A. The immediate cardiac depression by anesthetics in conscious dogs. Br J Anaesth 1969;41:86–93.

3. Thorburn J, Smith G, Vance JP, Brown DM. Effect of nitrous oxide on the cardiovascular system and coronary circulation of the dog. Br J Anaesth 1979;51:937–41.

4. Goldberg AH, Sohn YZ, Phear WPC. Direct myocardial effects of nitrous oxide. Anesthesiology 1972;37:373–80.

5. Eisele JH, Reitan JA, Massumi RA, Zelis RF, Miller RR. Myocardial performance and N_2O analgesia in coronary-artery disease. Anesthesiology 1976;44:16–20.

6. Eisele JH, Smith NT. Cardiovascular effects of 40% nitrous oxide in man. Anesth Analg 1972;51:956–63.

7. Smith NT, Eger EI, Stoelting RK, Wayne TF, Cullen D, Kadis LB. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 1970;32:410–21.

8. Bahlman SH, Eger EI, Smith NT, Stevens WC, Shakespeare TF, Sawyer DC, Halsey MJ, Cromwell TH. The cardiovascular effects of nitrous oxide-halothane anesthesia in man. Anesthesiology 1971;35:274–85.

9. Stoelting RK, Reis RR, Longnecker DE. Hemodynamic responses to nitrous oxide—halothane and halothane—in patients with valvular heart disease. Anesthesiology 1972; 37:430–5.

10. Lundborg RO, Milde JH, Theye RA. Effect of nitrous oxide on myocardial contractility of dogs. Can Anaesth Soc J 1966; 13:361–7.

11. Philbin DM, Foëx P, Drummond G, Lowenstein E, Ryder WA, Jones LA. Postsystolic shortening of canine left ventricle supplied by a stenotic coronary artery when nitrous oxide is added in the presence of narcotics. Anesthesiology 1985;62: 166–74.

12. Smith NT, Carbascio AN. The cardiovascular effects of N_2O during halothane anesthesia in the dog. Anesthesiology 1966; 27:560–6.

13. Coetzee A, Fourie P, Badenhorst E. Effect of halothane, enflurane and isoflurane on the end-systolic pressure-length relationship. Can J Anaesth 1987;34:351–7.

14. Bugge-Asperheim B, Leraand S, Kiil F. Local dimensional changes of the myocardium measured by ultrasonic technique. Scand J Clin Lab Invest 1969;24:361–71.

15. Forrester JS, Tyberg JV, Wyatt HL, Goldner S, Parmley WW, Swan HJC. Pressure-length loop: a new method for simultaneous measurement of segmental and total cardiac function. J Appl Physiol 1974;37:771–5.

16. Cochran WG, Cox GM. Experimental Designs. New York; Wiley, 1957:135–9.

17. Kaseda S, Tomoike H, Ogata I, Nakamura M. End-systolic pressure-length relations during changes in regional contractile state. Am J Physiol 1984;247:H768–74.

18. Kaseda S, Tomoike H, Ogata I, Nakamura M. End-systolic pressure-volume, pressure-length and stress-strain relations in the canine heart. J Appl Physiol 1984;294:H648–54.

19. Westerhof N, Elzinga G, Sipkema P. An artificial arterial system for pumping hearts. J Appl Physiol 1971;31:776–81.

20. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximum stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586–95.

21. Chamberlain JH, Seed RG, Chung DC. Effect of thiopentone on myocardial function. Br J Anaesth 1977;49:865–70.

22. Motomura S, Kissin JA, Massumi DF. Effect of fentanyl and N_2O on contractility of blood perfused papilary muscle of the dog. Anesth Analg 1984;63:1071–5.

23. Eddleman EE, Harrison WK, Jackson WDH, Taylor HL. A critical appraisal of ballistocardiography. Am J Cardiol 1972; 29:120–2.

24. Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. Circulation 1987;76:1422–36.

25. Strobeck JE, Sonnenblick EH. Pathophysiology of heart failure. In: HJ Levine, WH Gaasch, eds. The Ventricle. Basic and Clinical Aspects. Boston: Martinus Nijhoff, 1985:209–24.

26. Suga H, Sagawa K. Instantaneous pressure-volume relationship and their ratio in the excised left ventricle. Circ Res 1974;35:117–26.

27. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure-volume ratio: a new index of ventricular contractility. Am J Cardiol 1977;40:748–53.

28. Sagawa K. The end-systolic pressure-volume relation of the left ventricle: definition, modification and clinical use. Circulation 1981;63:1223–7.

29. Suga H, Sugawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973;32:314–22.

30. Maughan WL, Sunagawa K, Burkhoff D, Graves WL, Hunter WC, Sugawa K. Effect of heart rate on the canine end-systolic pressure-volume relationship. Circulation 1985;72:654–9.

31. Coetzee A, Fourie P, Badenhorst E. Response of the heart to acute hypertension during halothane, enflurane and isoflurane anesthesia. Anesth Analg 1987;66:1219–26.

32. Weber KT, Janicki WC, Shroff S, Pearlman ES, Fishman AP. The contractile behaviour of the heart and its functional coupling to the circulation. Prog Cardiovasc Dis 1982; 14:375–400.

33. Milnor W. Arterial impedance as ventricular afterload. Circ Res 1975;36:565–70.

34. O'Rourke MF. Vascular impedance in studies of arterial and cardiac function. Physiol Rev 1982;62:570–623.

35. Gersh BJ, Prys-Roberts C, Reuben SR, Schultz DL. The effect of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. II. Aortic input impedance, and the distribution of energy during ventricular ejection. Br J Anaesth 1972;44:767–75.

36. Balasaraswathi K, Kumar P, Rao TLK. El-Etr AE. Left ventricular end-diastolic pressure (LVEDP) as an index for nitrous oxide use during coronary artery surgery. Anesthesiology 1981;55:708–9.

37. Miller RD, Eger EI, Stevens WL, Gibbons R. Pancuronium induced tachycardia in relation to alveolar halothane, dose of pancuronium, prior atropine. Anesthesiology 1975;42:352–63.

38. Brown EM, Smiler BG, Plaza JA. Cardiovascular effects of pancuronium. Anesthesiology 1973;38:597–9.

39. Chidsey CA, Weinbach EC, Pool PE. Biochemical studies of energy production in the failing human heart. J Clin Invest 1966;45:40–50.

40. Toy SM, Melbin J, Noordegraaf A. Reduced models of arterial systems. IEEE Trans Biomed Eng 1985;32:174–6.

41. Westerhof N, Elzinga G, Sipkema P. An artificial system for pumping hearts. J Appl Physiol 1971;31:776–81.

42. Piene H. Pulmonary arterial impedance and right ventricular function. Physiol Rev 1986;66:606–52.

43. Calvin JE, Baer RW, Glantz SA. Pulmonary artery constriction produces greater RV dynamic afterload than lung microvascular injury in the open chested dog. Circ Res 1985; 56:40–56.

44. MacDonald DA. Blood Flow in Arteries. London: Edward Arnold, 1974:118–45.

45. Dujardin JL, Stone DN, Forcino CD, Paul LT, Pieper HP.

Effects of blood volume changes on characteristic impedance of the pulmonary artery. Am J Physiol 1982;242:197–202.

46. Yin FCP, Liu Z, Brin KP. Estimation of arterial compliance. In: Yin FCP, ed. Ventricular/Vascular Coupling. New York: Springer-Verlag, 1987:389.

47. Sunagawa K, Maughan L, Sagawa K. Optimal arterial resistance for the maximum stroke studed in the isolated canine left ventricle. Circ Res 1985;56:586–95.

Fifty-Nine Years Ago in

Anesthesia & Analgesia

B. C. Sword: The closed circle method of administration of gas anesthesia. Current Researches in Anesthesia and Analgesia: 1930;9:198–202.

This paper introduces one of the more fundamental changes in the history of equipment used for the administration of inhalation anesthesia. Only shortly before this paper came out, the principles of closed circuit anesthesia were established by Ralph Waters at the University of Wisconsin. What Waters did was to incorporate a soda lime cannister for absorption of carbon dioxide as developed by D. E. Jackson at the University of Circinnati into a system in which the patient exhaled through the cannister into a reservoir bag and then inhaled the exhaled gas back through the cannister. This to-and-fro system made it possible to give closed circuit inhalation anesthesia, a major advance. The to-and-fro system had disadvantages, though. One was that the soda lime cannister was relatively large. It also had to be near the mouth to avoid intolerable increases in mechanical deadspace. The result was equipment not only bulky and difficult to handle but also in the way during certain surgical procedures. What Sword, at the time an anesthetist in New Haven, Connecticut, did was to design a closed system that was easier to handle and did not get in the way. After consultation with Yandell Henderson, Professor of Applied Physiology at Yale, Sword came up with a circuit in which respired gases passed not back and forth through a soda lime cannister but, instead, into one end of a cannister and out the other end. Breathing tubes with one-way flutter valves went from the inlet and outlet ports of the cannister to a Y-piece that fit into the anesthesia face mask. This allowed the carbon dioxide absorber, along with the reservoir breathing bag, to be placed at some considerable distance from the patient. Sword's system was immediately seized upon by his fellow anesthetists. With the help of Richard Foregger, a pioneer in the mass production of quality anesthesia machines, the closed circle system soon displaced to a large degree not only the to-and-fro system of Waters but also the demand-flow systems of McKesson. The popularity of the circle system, closed or semi-closed, continues to this day, especially in North America. In the United Kingdom and parts of Europe, semiopen and nonrebreathing circuits have continued to be as popular or more popular than circle systems, but neither circuit has totally replaced the other on either side of the Atlantic.

Spinal Cord Distribution of ³H-Morphine after Intrathecal Administration: Relationship to Analgesia

Yuji Nishio, MD, Raymond S. Sinatra, MD, PhD, Luke M. Kitahata, MD, PhD, and J. G. Collins, PhD

NISHIO Y, SINATRA RS, KITAHATA LM, COLLINS JG. Spinal cord distribution of ³H-morphine after intrathecal administration: relationship to analgesia. Anesth Analg 1989;69:323–7.

The distribution of intrathecally administered ³H-morphine was examined by light microscopic autoradiography in rat spinal cord and temporal changes in silver grain localization were compared with results obtained from simultaneous measurements of analgesia. After tissue processing, radioactivity was found to have penetrated in superficial as well as in deeper layers (Rexed lamina V, VII, and X) of rat spinal cord within minutes after application. Silver grain density reached maximal values at 30 min in every region of cord studied. Radioactivity decreased rapidly between 30 min and 2 hr and then more slowly over the next 24 hr. In rats tested for responses to a thermal stimulus (tail flick test), intrathecal administration of morphine (5 and 15 µg) resulted in significant dose dependent analgesia that peaked at 30 min and lasted up to 5 hr (P < 0.5). There was a close relationship between analgesia and spinal cord silver grain density during the first 4 hr of the study. It is postulated that the onset of spinal morphine analgesia depends on appearance of molecules at sites of action followed by the activation of anti-nociceptive mechanisms.

Key Words: ANALGESICS—morphine. ANESTHETIC TECHNIQUES—spinal, morphine. SPINAL CORD, LAMINAE OF DORSAL HORN—morphine.

The noxiously evoked activity of nociceptive neurons in the lumbar dorsal horn is selectively suppressed by intrathecally (1,2), iontophoretically (3), as well as systemically (4,5) administered opioids. Light microscopic autoradiography (6,7) and histochemical binding techniques have revealed that opiate receptors are highly concentrated in the substantia gelatinosa, a major site for early integration of nociceptive input. Taken together, this evidence strongly suggests that the dorsal horn is an important site of action for opioid analgesia and for the clinical effectiveness of spinal opioids in treatment of acute and chronic pain (8).

Mechanisms responsible for spinal opioid analgesia, especially the sequence by which drugs are taken up by, distributed to, and eliminated from the sites of activity in the dorsal horn remain to be clarified. In this regard, a temporal evaluation of spinal opioid pharmacodynamics in the spinal cord might provide insights into mechanisms underlying opioid analgesia. Although Schubert et al. (9) demonstrated the time course of radiolabeled opioid penetration into rat periventricular cortex after intraventricular application, a detailed evaluation has not been performed at the spinal level. The following investigation was designed to examine the uptake and distribution of radiolabeled morphine into the spinal cord after intrathecal application, and in a temporal fashion, to compare the time course of penetration and localization with responses to a peripheral noxious stimulus.

Methods

1. Preparation

After approval of the University Animal Investigation and Radiation Safety Committees, polyethylene catheters (PE-10) were inserted intrathecally through the T1–2 intervertebral space of 30 female (200–220 g)

Sprague-Dawley rats utilizing halothane anesthesia and a technique modified from Dib (10). The distal catheter tip was carefully advanced and positioned immediately adjacent to the lumbar enlargement (T-12 level), whereas the proximal portion was sutured to fascia and skin in the animal's neck. After a 7-day recovery period, animals demonstrating any neurological deficit were eliminated from the study. Catheter patency was maintained with daily heparin-saline solution flushes, and intrathecal placement was tested the day before tail-flick testing with 4% lidocaine (10 μL). Only animals having complete bilateral hind paw paresis after lidocaine injection were used in this study.

2. Tail-Flick Test

After baseline (intrathecal saline) tail-flick testing utilizing a 300 W lamp thermal stimulus (11), animals were divided into two treatment groups and given either 5 μg or 15 μg of morphine in 10 μL of saline solution through the indwelling intrathecal catheter followed by a 10 μL saline solution flush. Fifteen rats in each group were then retested at 5, 10, 30, 60, 120, 180, 240, 300, min, 24 and 48 hr after drug administration. At each interval, tail-flick latency represented the summed average of three measured responses. Cut-off time was limited to 6.5 sec to prevent thermal injury. Student's t-test was used for statistical analysis with $P < 0.05$ considered statistically significant.

3. Autoradiography

Forty-eight hours after completion of tail-flick testing, 18 animals received 5 μCi/3 μg of ^{3}H-morphine sulfate (480 μCi/μM) with 15 μg of unlabeled morphine in 10 μL of saline solution through the intrathecal catheter followed by 10 μL saline solution flush. Three animals were killed with 100% nitrous oxide and 5% halothane (death occurred within approximately 2 min) at each of the following time intervals: 5 and 30 min, 2, 5, 24, and 48 hr. Lumbar vertebral bone including spinal cord was quickly removed and frozen rapidly in chilled isopentane (−70°C). The frozen lumbar enlargement of the cord was carefully removed and cut in 2–3-mm thick segments. Spinal cord segments were then quickly sectioned (8 μm) with a cryostat (IEC-CTF Cryotome-Cryostat) at −15°C. Frozen sections were dried and mounted on slides previously coated by Ilford K-5 emulsion and then placed in light-tight boxes with desiccant. Slide boxes were then stored in a desiccator (at −15°C) for a 30-day exposure period.

Development of autoradiographs was performed with Kodak D-19, followed by stop bath for 30 sec and Kodak acid fixer for 5 min. After several rinses in distilled water, tissues were stained with 2% cresyl violet and examined with a light microscope with use of oil immersion optics (1000×). The number of silver grains in 625 μm^2 regions of rat spinal lamina I, II, III, V, X, ventral horn and white matter (posterior and lateral columns) were counted At each region, the number of grains in three separate randomly selected areas were counted and the average was taken as a grain density in that region. Student's t-test was used for statistical analysis with $P < 0.05$ considered significant.

Results

Tail-Flick

A baseline tail-flick latency of 3.7 sec in saline solution treated controls was significantly delayed 5 min after intrathecal injection of either 5 or 15 μg of morphine. After administration of the 15-μg dose, a significant delay of tail-flick latency was noted at 5 min and maintained at 5 hr but not at 24 hr or 48 hr (Figure 1). A maximal effect (stimulus duration reached cut-off time) was seen from 30 min to 2 hr. After administration of the 5 μg dose, statistically significant inhibition of the tail-flick response was seen between 5 min and 3 hr ($P < 0.05$); however, a maximal effect was not achieved. Tail-flick responses returned to baseline values 4 hr after administration of the 5 μg dose.

Autoradiography

The time required for harvesting the spinal cord was approximately 3 min. The catheter tip was found to be adjacent to the lumbar enlargement in all animals. Other than a fibrotic reaction around the catheter, there were no histopathological changes. Autoradiographic background was 3.6 ± 0.7 grains/625 μm^2 in gray matter, and chemographic artifacts were not observed.

At the 5-min time point, silver grains were detected throughout the length of the excised spinal cord; however, the highest grain density was concentrated at superficial sites (pia-arachnoid, Lamina I, II) immediately adjacent to the catheter tip (Figure 2). Peak density of silver grains was reached at 30 min in every area sampled. At this time, highest grain density was again observed in superficial layers of cord; however, moderate amounts were present in deeper

Figure 1. Time course of rat tail-flick response to different doses (5, 15 μg) of intrathecally administered morphine. Ordinate is response latency in seconds. Abscissa is time in hours. Values shown represent mean ± SEM of three measured responses in 15 animals at each time interval: * indicates statistically significant difference compared with values in controls (P < 0.05).
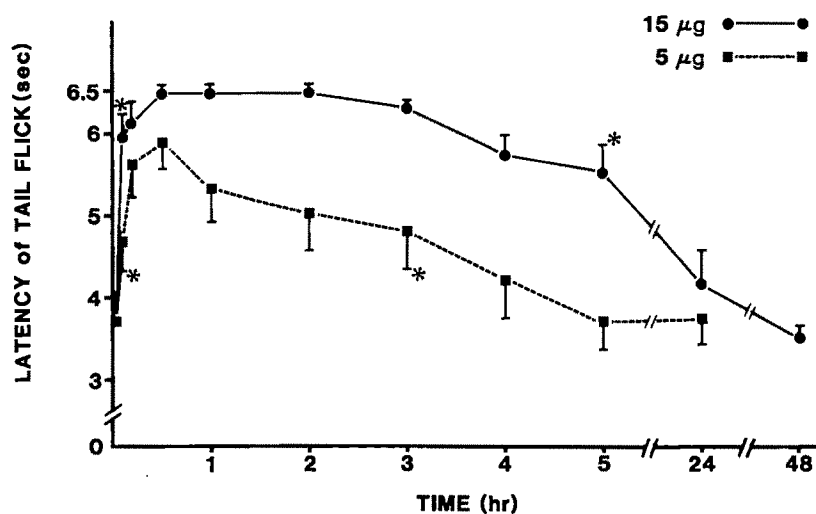
Figure 2. Graphic demonstration of penetration and elimination of radiolabeled morphine in two different areas (Rexed lamina II and V) of rat spinal cord. Ordinate is mean number of silver grains in nine separate 625 μm² areas, counted in three different animals. Abscissa is time in minutes or hours.
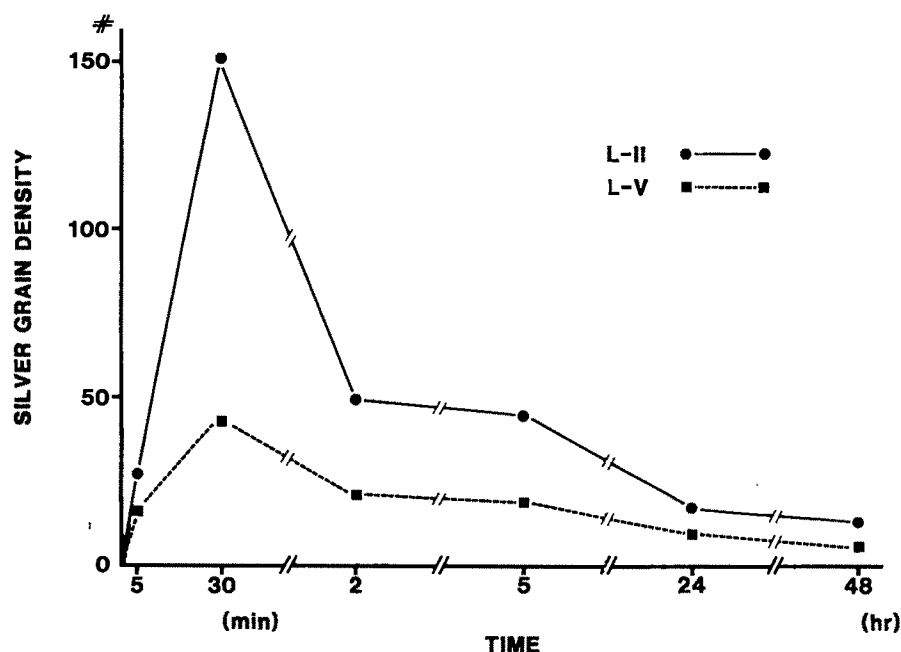
layers (lamina V, VII, and X) and gray matter, whereas lowest amounts were noted in white matter (Figure 3). This pattern of distribution was maintained until the end of the experiment. Grain densities in most areas decreased rapidly during the next 90 min then more slowly over the next 24 hr.

Discussion

The onset of pharmacologic activity after spinal opioid administration has been found to correlate well with the lipid partition coefficient of the agent utilized. In this regard, the slow onset of spinal morphine analgesia noted in behavioral (12,13) or neuro-

physiologic (1,2) studies has been related to sequestration of morphine in CSF and delayed penetration to sites of action in the spinal cord. Schubert et al. (9) supported this hypothesis by demonstrating that the "radioactivity front" of intraventricularly administered morphine advanced slowly into the cerebral wall (800 μm at 7 min, 1200 μm at 25 min). However, using a higher resolution ³H tracer, the present investigation could not appreciate a "radioactivity front" or any noticeable delay in penetration. Instead, radioactivity was found to be widely dispersed throughout the cord within a few minutes after application. This discrepancy may be related to methodological differences between the two studies,
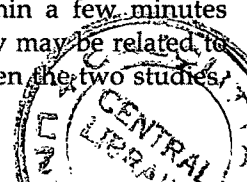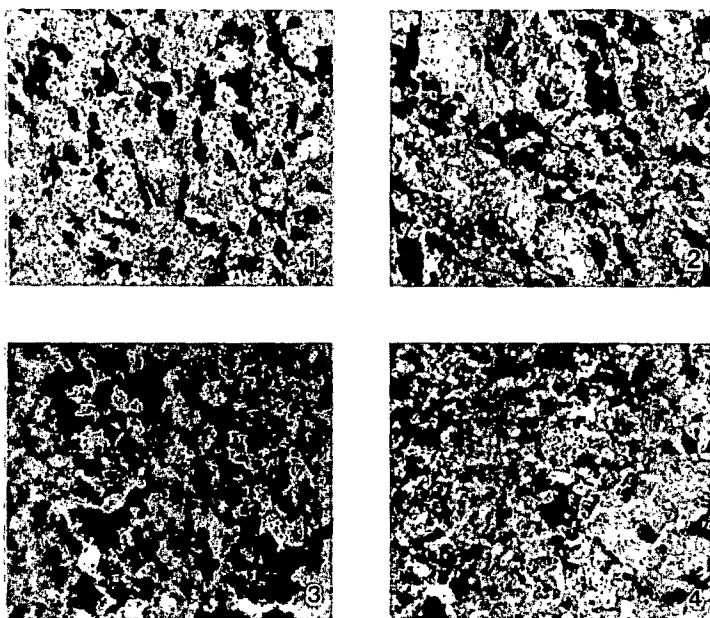
Figure 3. Photographic illustrations of light microscopic (400×) autoradiograms taken from 1) lamina II, 2) lamina V, 3) lamina X, and 4) ventral horn of rat spinal cord 30 min after application of ³H-morphine. Silver grains appear as pin-point sized dots, whereas larger dark-stained structures are neuronal and glial cells.

including dose, concentration of radioactive substance, and anatomical structure. In any event, our findings indicate that morphine penetrates spinal tissue rapidly, is present at sites of action within minutes of application, and onset of maximal change in tail-flick latency occurred at the time of maximal silver grain accumulation. In this regard, a slower onset of spinal analgesia with morphine reported in humans may not be related entirely to delayed penetration of morphine molecules into cord but instead may be due to possible delays in activating a critical number of opioid receptors (14).

A relationship between maximal accumulation of dorsal horn silver grain and peak effect suggested that this region of the cord is a major site of action of spinal opioid analgesia and that a critical concentration of morphine molecules is required to achieve peak analgesic efficacy. Although the present evaluation cannot comment on specific opiate receptor binding, high grain accumulation in superficial layers is in accord with previous autoradiographic studies that demonstrated significant uptake in this region and in substantia gelatinosa (6,14,15). Because metabolism of drug would be expected to be minimal at early observation periods, the majority of silver grains localized to dorsal horn at this time represent morphine molecules.

The long duration of spinal morphine analgesia noted in clinical studies has been related to the vascular endothelial barrier that inhibits reuptake of morphine (4,13,16). Investigations demonstrating persistence of spinally applied morphine in humans (16) and animal (17) CSF support this hypothesis. Although we noticed a decline in silver grain density

after 4 hr, radioactivity still remained in the cord 24 hr after administration. Because the duration of spinal analgesia was relatively short, it is likely that the majority of grains observed at later time intervals represents nonspecific binding of morphine or its metabolites, or both. Our finding of 4–6 hr of spinal analgesia agrees with recent studies in rats reporting similar duration after intrathecal (12) and epidural (18) administration of morphine.

In conclusion, the present study demonstrates that penetration of morphine into various layers of the spinal cord correlates closely with the time course of analgesia. Persistence of morphine in rat spinal cord up to 24 hr did not appear to correlate with a prolonged duration of analgesia and may represent nonspecific binding.

References

1. Homma E, Collins JG, Kitahata LM, et al. Suppression of noxiously evoked WDR dorsal horn neuronal activity by spinally administered morphine. Anesthesiology 1983;58:232–6.

2. Suzukawa M, Matsumoto M, Collins JG, et al. Dose-response suppression of noxiously evoked activity of WDR neurons by spinally administered fentanyl. Anesthesiology 1983;58:510–3.

3. Calvillo O, Henry JL, Neuman RS. Actions of narcotic analgesics and antagonists on spinal units responding to natural stimulation in the cat. Can J Physiol Pharmacol 1979;57:652–63.

4. Kitahata LM, Kosaka Y, Taub A, et al. Lamina-specific suppression of dorsal horn unit activity by morphine sulfate. Anesthesiology 1974;41:39–48.

5. LeBars D, Menetrey D, Conseiller C, Besson JM. Depressive effects of morphine upon lamina V cells activities in the dorsal horn of the spinal cat. Brain Res 1975;98:261–77.

6. Atweh SH, Kuhar MJ. Autoradiographic localization of opiate receptors in rat brain. I. Spinal cord and lower medulla. Brain Res 1977;124:53–67.

7. Herkenham M, Pert CB. Light microscopic localization of brain opiate receptors: a general autoradiographic method which preserves tissue quality. J Neurosci 1982;2:1129-49.

8. Wang JK, Nauss LA, Thomas TE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979;50:149-51.

9. Schubert P, Teschemacher H, Kreutzberg GW, et al. Intracerebral distribution pattern of radioactive morphine and morphine-like drugs after intraventricular and intrathecal injection. Histochemie 1970;22:277-88.

10. Dib B. Intrathecal chronic catheterization in the rat. Pharmacol Biochem Behav 1984;20:45-8.

11. D'amour FE, Smith DL. A method for determining loss of pain sensation. J Pharmacol Exp Ther 1941;72:74-9.

12. Yaksh TL, Noveihed RY, Durant PAC. Studies of the pharmacology and pathology of intrathecally administered 4-anilinopiperidine analogues. Anesthesiology 1986;64:54-66.

13. Herz A, Teschmacher HJ. Activity and sites of anti-nociceptive action of morphine-like analgesics kinetics of distribution following intravenous, intracerebral and intraventricular application. Adv Drug Res 1971;6:79-119.

14. Wamsley JK, Zarlin MA, Young WS III, et al. Distribution of opiate receptors in the monkey brain: an autoradiographic study. Neuroscience 1982;7:593-613.

15. Gouarderes C, Cros J, Quirion R. Autoradiographic localization of mu delta and kappa opioid receptor binding sites in rat and guinea pig spinal cord. Neuropeptides 1985;6:331-42.

16. Nordberg G, Hedner T, Mellstrand T, et al. Pharmacokinetic aspects of intrathecal morphine analgesia. Anesthesiology 1984;60:448-54.

17. Gustafsson LL, Post C, Edvardsen B, et al. Distribution of morphine and meperidine after intrathecal administration in rat and mouse. Anesthesiology 1985;63:483-9.

18. Van den Hoogen RH, Colpaert FC. Epidural and subcutaneous morphine, meperidine, fentanyl, and sufentanil in rat. I: Analgesia and other in vivo effects. Anesthesiology 1987;66:186-94.

The Effects of Oral Transmucosal Fentanyl Citrate Premedication on Preoperative Behavioral Responses and Gastric Volume and Acidity in Children

Theodore H. Stanley, MD, Basil C. Leiman, MD, Narinda Rawal, MD, PhD,

Marco A. Marcus, drs, Marjolein van den Nieuwenhuyzen, drs, Andrew Walford, MD,

Leslie H. Cronau, MD, PhD, and Nathan L. Pace, MD

STANLEY TH, LEIMAN BC, RAWAL N, MARCUS MA, VAN DEN NIEUWENHUYZEN M, WALFORD A, CRONAU LH, PACE NL. The effects of oral transmucosal fetanyl citrate premedication on preoperative behavioral responses and gastric volume and acidity in children. Anesth Analg 1989;69:328–35.

The authors compared the safety, efficacy, and effects on gastric volume and pH of oral transmucosal fentanyl citrate (OTFC) premedication and of placebo lollipop and no premedication in 55 children undergoing elective operations. The patients were randomly assigned to receive no premedication (group A, N = 18); OTFC containing 15–20 µg/kg of fentanyl citrate (group B, N = 18); or a placebo lollipop (group C, N = 19). Activity (sedation) and anxiety scores, vital signs (including systolic and diastolic arterial blood pressures, heart and respiratory rates), and pulse oximetry determined oxygen saturation were measured before and at 10-min intervals after premedication until the patients were taken to the operating room. Gastric contents were aspirated via an orogastric tube and analyzed for volume and pH after induction of anesthesia. Quality of induction and recovery were evaluated using scoring schedules; recovery times were measured and side effects recorded. OTFC was readily accepted and provided levels of sedation and anxiolysis significantly greater after 10 min than after no premedication or the placebo lollipop. Arterial blood pressures, heart rate, and oxygen saturations were not different among the three groups. In patients given OTFC, respiratory rates were significantly lower after 10 min than they were in patients having no premedication. When compared to patients having no premedication, patients having OTFC had slightly increased gastric volumes (14.6 ± 10 vs 7.6 ± 5.3 mL, mean ± SD). Patients having a placebo lollipop had similar gastric volumes (15.6 ± 13.5 mL) as those having OTFC. The three groups had similar gastric pH's (1.69 ± 0.31, 1.92 ± 0.53 and 1.72 ± 0.28, mean ± SD, groups A, B, and C, respectively). Induction and recovery evaluations and recovery times were also similar in the three groups. OTFC was associated with a 50% incidence of mild, nondisturbing, preoperative facial pruritus and a higher overall incidence of postoperative nausea (44%) than was premedication with the placebo lollipop (16%) or no premedication (0%). The results demonstrate that OTFC is readily accepted, safe, and more effective than no premedication or premedication with a placebo lollipop, and does not affect gastric pH but does increase gastric volume.

Key Words: ANALGESICS, FENTANYL. PREMEDICATION, ORAL TRANSMUCOSAL—fentanyl. ANESTHESIA, PEDIATRIC.

Fentanyl incorporated into a candy matrix and formulated in a lollipop for oral transmucosal absorption is a novel method of administering premedication in children (1–3). Although previous studies have shown that oral transmucosal fentanyl citrate (OTFC) premedication produces dose dependent increases in sedation and analgesia in adult volunteers (1) and sedation and anxiolysis in children before operation (2,3), the evaluations were open (not double-blinded), and the influence of OTFC on gastric volume and acidity was not evaluated.

The purpose of this study was to compare and contrast the effects of OTFC and placebo lollipop (no fentanyl) premedication with no premedication on the gastric volume and acidity of children about to

undergo outpatient surgical procedures. The study was accomplished using a randomized and (when appropriate) double-blind approach. Respiratory, sedative, and anxiety evaluations were also performed and recovery times and side effects determined.

Methods

Approval was received from the Food and Drug Administration and the Herman Hospital Human Study Review Board, and written consent was obtained from the parents of 64 ASA physical status 1–2 children aged 5–12 years scheduled for a variety of elective orthopedic, ophthalmologic, otolaryngologic, or urologic outpatient or "same-day-admit" operations. After consent was obtained, the children were randomly assigned to one of three groups: group A received no premedication; group B received fentanyl citrate (15–20 μg/kg) (a previous investigation (2) had determined that 15–20 μg/kg of fentanyl citrate was an optimal dose range of OTFC for premedication in children) in a candy lollipop (OTFC); and group C received a lollipop which looked and tasted exactly like those in group B except it contained no drug (a placebo). The lollipops were made by heating a candy base and (in group B) adding 200, 250, 300, 400, 500, 700, 800, 900, or 1000 μg of fentanyl citrate crystals. Following mixing, the candy (for group C) and the candy-fentanyl mixture (for group B) were poured into molds, a stick added and the lollipop allowed to cool and harden before removal from the molds. Placebo and fentanyl containing lollipops were the same size, 1.6 mL.

The study was double-blinded with respect to the placebo vs active (fentanyl-containing) lollipops; however, investigators performing holding-room evaluations knew group A patients were a control group and had received no premedication.

Approximately 30 to 60 min before the scheduled beginning of the operation, each child (accompanied by his or her parents) was brought to the preoperative holding area adjacent to the operating room. Following examination of the patient's oral mucosa, his or her baseline systolic and diastolic arterial blood pressures, heart rate, respiratory rate, and oxygen saturation were measured by a standard manual pediatric blood pressure cuff, radial artery palpation, observation of the chest wall, and use of a Criticare Systems Model 501 pulse oximeter, respectively. The patients then received either OTFC, the placebo lollipop, or no premedication. Children in groups B and C were asked to rapidly suck on the lollipop without

Table 1. Scoring Schedules for Evaluation of Preoperative Activity (Sedation), Anxiety, the Level of Cooperation prior to Induction of General Anesthesia, and Reactivity during Emergence from General Anesthesia

Preoperative activity
1 = Asleep; not readily arousable
2 = Asleep; responds slowly to verbal commands
3 = Drowsy; readily responds to verbal commands
4 = Awake; calm and quiet
5 = Awake and active
Preoperative anxiety
1 = None
2 = Little (demonstrates some fear or uneasiness but does not cry)
3 = Moderate (clearly fearful, cries but becomes quiet with reassurance)
4 = Excessive (crying, uncooperative, does not become quiet with reassurance)
Preinduction cooperation
1 = Excellent (none of the conditions listed below as A, B, or C)
2 = Good (one of conditions A, B, or C)
3 = Fair (two of conditions)
4 = Poor (all three of conditions A, B, and C)
    A. Crying
    B. Need for restraint
    C. Avoidance
Emergence
1 = Excellent (quiet)
2 = Good (occasional crying)
3 = Fair (crying, but able to be quieted)
4 = Poor (thrashing, not to be quieted)

biting or chewing it, and the time required for complete consumption of the candy was recorded.

Oxygen saturation was continuously measured and heart rate, systolic and diastolic blood pressures and respiratory rate remeasured every 10 min throughout the preanesthetic evaluation period until the children were taken to the operating room. Activity and anxiety scores (Table 1) evaluating the effectiveness of the premedication were also determined at baseline (prior to premedication administration) and every 10 min thereafter until the children were taken to the operating room. Children taken to the operating room within 30 min of receiving premedication were not considered suitable for evaluation. Before departure to the operating room, each patient's oral mucosa was reexamined.

Anesthesia was induced with halothane (1–3%) and nitrous oxide (N_2O) (60%) in oxygen via a face mask by an anesthesiologist unaware of the group allocation of the patient. Ventilation was at first spontaneous, then assisted, and finally controlled as the patient lost consciousness. Following loss of consciousness an intravenous infusion of 5% dextrose and 0.25% normal saline was started in a hand or arm vein. The trachea was intubated without the use of a muscle relaxant unless laryngeal exposure

was difficult or other anatomic considerations suggested that paralysis would significantly facilitate tracheal intubation. In these circumstances, atracurium (0.5 mg/kg, IV) was used for relaxation. The ease and quality of anesthetic induction was evaluated according to an anesthetic induction scoring scale (Table 1).

Assessment of the volume and pH of gastric contents was based on the method of Salem et al. (4) and others (5,6). Two to five minutes after the endotracheal tube was taped in place an orogastric tube was passed into the stomach and the gastric contents aspirated by wall suction into a mucus trap. Manual pressure on the upper abdomen was used to assist gastric emptying. The position of the catheter was verified by auscultation during insufflation of a few milliliters of air. Volume of the gastric aspirate was measured in a calibrated buret and pH was determined by a Corning-Scientific Instruments pH meter. Volumes of gastric contents were expressed as mL per kilogram body weight. The incidence of patients with pH levels higher than 2.5 was determined. Patients in whom no gastric contents could be obtained were designated "dry cases." Those patients considered dry cases and those having a pH higher than 2.5 were designated "safe cases," and their frequency in the three groups were compared utilizing the χ^2 test.

Anesthesia was maintained with halothane (0.1–2.5%) or isoflurane (0.1–2.0%) and N_2O (60%) in oxygen in concentrations adequate to keep systolic blood pressure within 20% of preoperative values. No opiates, antiemetics or intravenous anesthetics were used; muscle relaxants were used after tracheal intubation if clinically indicated. Ventilation was usually controlled until 10–20 min before the end of the operation, when halothane or isoflurane was decreased or discontinued, and spontaneous ventilation was resumed. After termination of all anesthetics, patients' tracheas were extubated when they responded to the tracheal tube, the respiratory rate was >12 breaths/min, and tidal volume was considered clinically to be adequate.

Emergence from anesthesia was evaluated upon arrival in the recovery room and every 30 min thereafter using an emergence scoring scale (Table 1). Times to awakening (as measured from discontinuation of all inhalation anesthetics until spontaneous eye opening first occurred) and first response to verbal commands (as measured from termination of all inhalation anesthetics until eye opening first occurred upon command) were evaluated every 5 min in the recovery room and recorded. Intravenous opiates (morphine 0.5–1.0 mg or meperidine 5–10 mg) were requested by the recovery room nurses (who were unaware of the premedication used) for

Table 2. Demographic Data in 55 Children Receiving Premedication with Oral Transmucosal Fentanyl Citrate (OTFC), a Placebo Lollipop or No Premedication (Mean ± Standard Error of the Mean)

	Group A No premed	Group B OTFC	Group C Placebo
Gender (M/F)	12/6	7/11	8/11
Age (yr)	7.2 ± 0.7	6.9 ± 0.6	7.6 ± 0.4
Weight (kg)	26.8 ± 2.4	25.5 ± 1.4	28.4 ± 1.9
Height (cm)	126.1 ± 4.5	123.1 ± 2.9	128.8 ± 2.3
Duration of anesthesia (min)	46.7 ± 7.6	68.3 ± 7.6	69.8 ± 16.7

control of moderate or severe postoperative pain (as determined by an anesthesiologist uninvolved with the study). Patients were discharged from the recovery room when they achieved a score of 10 using the Aldrete postanesthetic recovery score (7). Recovery time, defined as time from arrival in the recovery room to fulfillment of discharge criteria, was recorded. The incidences and times of occurrence of pruritus and nausea (as volunteered by the patient) and vomiting were recorded in the preoperative holding area, operating room, and recovery room, and for 3 hr postoperatively or until outpatients were discharged.

Data were analyzed for statistical significance using a one-way analysis of variance (ANOVA) for age, weight, height, vital signs, and oxygen saturation; individual comparisons were performed by the Duncan multiple range test. Gender, race, type of operation, and ASA physical status were compared using χ^2 tests. Changes with time for vital signs were evaluated by repeated measures ANOVA with polynomial contrasts for linear trends. Activity ratings were analyzed at each evaluation period and were grouped as asleep/drowsy (activity scores 1–3) vs awake (scores 4 and 5) due to small numbers in most categories; activity and anxiety ratings were analyzed at each evaluation period using a Kruskal-Wallis nonparametric ANOVA with Dunn's multiple range test comparisons. Changes in anxiety and activity levels from baseline were analyzed using χ^2 procedures. Gastric volume and pH data were analyzed using Kruskal-Wallis ANOVA. Duration of anesthesia and recovery room data (emergence times and side effect incidence) were analyzed by Kruskal-Wallis ANOVA with Dunn's multiple comparisons. The majority of analyses were performed with the SYSTAT statistical package for the IEM-PC. $P < 0.05$ was considered statistically significant.

Results

Data from nine of the 64 patients entered into the study were not evaluated because they did not re-
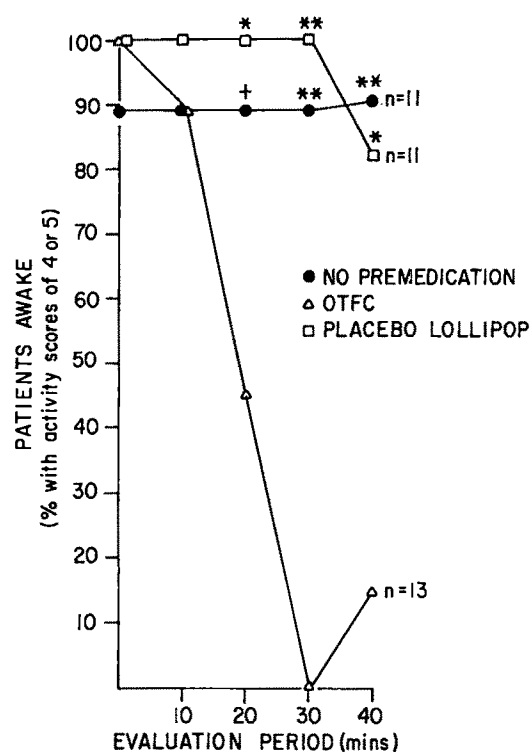
Figure 1. Percent of children awake (activity scores of 4 or 5) as a function of time. Except at 40 min there were 18 patients receiving no premedication, 18 receiving OTFC for premedication, and 19 receiving a placebo lollipop for premedication. $\dagger P < 0.05$, $*P < 0.01$, $**P < 0.001$ compared to OTFC, Kruskal-Wallis test with Dunn's multiple comparisons.

Figure 2. Percent of children with little or no anxiety (anxiety scores 1 or 2) as a function of time. Except at 40 min there were 18 patients receiving no premedication, 18 receiving OTFC for premedication, and 19 receiving a placebo lollipop for premedication. $\dagger P < 0.05$, $*P < 0.01$, $**P < 0.001$ compared to OTFC, Kruskal-Wallis test with Dunn's multiple comparisons.

main in the holding area for at least 30 min (N = 8), or received two lollipops (N = 1). Of the 55 children suitable for evaluation, 18 received no premedication (group A), 18 received OTFC (group B), and 19 received a placebo lollipop (group C). The three groups were similar with respect to age, weight, height, gender distribution (Table 2), distribution of the surgical procedures performed, ASA physical status distribution, baseline vital signs and oxygen saturation, and duration of anesthesia. All patients in groups B and C readily accepted their lollipops. Patients given OTFC required 17 ± 8 min (mean ± standard deviation; range 8–36 min), and patients receiving a placebo lollipop required 11 ± 4 min (range 5–23 min) for complete consumption of the lollipops. The difference in consumption times was statistically different. Oral mucosa was normal before and after lollipop consumption in all patients.

The 55 children completing the study had preoperative evaluations for at least 30 min after baseline and until they were brought to the operating room. The number of children evaluated in the three groups decreased with each additional 10-min interval after 30 min as increasing numbers of patients were called to the operating room. Evaluations at 40 min after

baseline included 35 patients (11, 13, and 11 in groups A, B, and C, respectively) whereas 50 and 60 min after baseline 25 (7, 10, and 8, in groups A, B, and C, respectively) and 16 (7, 6, and 3 in groups A, B, and C, respectively) patients were evaluated.

Figures 1 and 2 plot the percent of patients awake (activity scores of 4 or 5) and calm (little or no anxiety; anxiety scores of 1 or 2) as a function of time. Evaluations past 40 min after baseline are not included in the figures because the number of patients within each group decreased to less than half of those entered into the study. Overall analysis of the proportions of patients that were sleepy or drowsy (activity scores 1, 2, or 3) vs awake were comparable among groups at baseline but patients receiving OTFC were significantly less active than the other two groups after 20, 30, and 40 min (Figure 1). Analysis of change in activity from baseline indicated that patients having OTFC were significantly less active than those having no premedication or a placebo lollipop 10, 20, 30, and 40 min after baseline (Figure 3). There was no significant difference in the activity scores of patients receiving no premedication (group A) or a placebo lollipop (group C) at any time
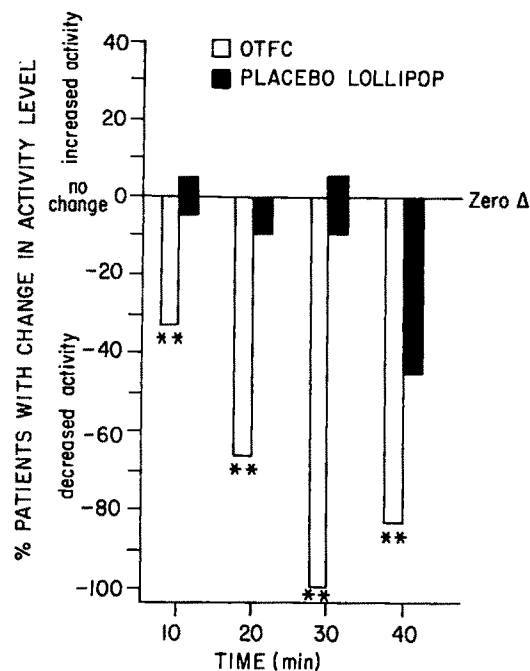
Figure 3. Percent of patients with changes in activity level as a function of time. Except at 40 min (when 11 patients each were in groups A and C and 13 in group B) there were 18 patients receiving no premedication, 18 receiving OTFC for premedication, and 19 receiving a placebo lollipop for premedication. **$P < 0.001$, x^2 analysis.

Figure 4. Percent of patients with changes in anxiety level as a function of time. Except at 40 min (when 11 patients each were in groups A and C and 13 in group B) there were 18 patients receiving no premedication, 18 receiving OTFC for premedication, and 19 receiving a placebo lollipop for premedication. *$P < 0.01$, **$P < 0.001$, x^2 analysis.

(Figure 1). Patients in groups A and C had significantly ($P < 0.001$) higher activity scores (less sedation) at the time of peak sedation.

Patients receiving OTFC (group B) had significantly lower anxiety ratings (i.e., were less anxious) than patients receiving a placebo (group C) at 20 min and than groups A and C at 30 and 40 min after baseline recordings (Figure 2). Patients given OTFC had significantly greater decreases in anxiety than those having no premedication or a placebo lollipop 20, 30, and 40 min after baseline (Figure 4). There was no significant difference in the anxiety scores of patients in groups A and C at any time (Figure 2). Patients in groups A and C had significantly higher anxiety scores (more anxiety) at the time of lowest anxiety.

Induction scores in the three groups were similar. Gastric volume and pH data were obtained from 53 patients and are given in Tables 3 and 4. No data could be obtained from two of the 18 patients evaluated in group A because of technical difficulties in insertion of the stomach catheter. While overall comparison of the three groups yielded no statistical difference in the pH values or volumes of the gastric aspirates, patients in group B (OTFC) had slightly but significantly ($P < 0.046$) higher gastric volumes when compared to patients in group A, whether evaluated

in absolute volume or volume/kilogram body weight (Tables 3 and 4). Gastric volume diferences between groups A and C and groups B and C were not statistically different. Insufficient gastric juice to measure pH prevented data collection from six patients, three each from groups A and B. The incidence of these "dry" cases was not significantly different among the three groups. The numbers and percentages of patients with gastric pH's above 2.5 (after excluding "dry" cases) were also similar in the three groups (ranging from 5%–11%) and are shown in Table 4. Likewise, the percent of patients with gastric pH's below 2.5 (72%–95%) and the percent of "safe cases" (5%–28%) were not significantly different among the three groups, Table 4.

There were no differences in the three groups in systolic and diastolic arterial blood pressures, heart rate, and oxygen saturation at any time in the holding area. Repeated measures ANOVA and tests for linear trends demonstrated a slight but statistically significant ($P < 0.025$) decrease of systolic arterial blood pressure over time in groups A and C but not group B. Patients receiving OTFC had significantly lower respiratory rates at all evaluations after 10 min (Figure

Table 3. Gastric Volume and pH Data in 53 Children Given Premedication with Oral Transmucosal Fentanyl Citrate (OTFC), a Placebo Lollipop or No Premedication

	Group A No premed	Group B OTFC	Group C Placebo
Gastric volume (mL)			
N	16	18	19
Mean	7.6	14.6*	15.6
Standard deviation	5.3	10.0	13.5
Median	7.5	15.0	10.0
Range	0–20	0–35	2–50
Gastric pH			
N	13	15	19
Mean	1.69	1.92	1.72
Standard deviation	0.31	0.53	0.28
Median	1.64	1.70	1.62
Range	1.37–2.62	1.43–3.34	1.46–2.73

$*P < 0.05$ Kruskal-Wallis ANOVA with Dunn's multiple comparison when compared to group A.

Figure 5. Respiratory rate as a function of time (mean ± SEM). Except at 40 min there were 18 patients receiving no premedication, 18 patients receiving OTFC for premedication, and 19 receiving a placebo lollipop for premedications. $+P = 0.05$, when compared to the other two groups, ANOVA with Duncan's multiple range test.

Table 4. Gastric Volume and pH Data in 53 Children Receiving Premedication with Oral Transmucosal Fentanyl Citrate (OTFC), a Placebo Lollipop or No Premedication

	Group A No premed	Group B OTFC	Group C Placebo
N	16	18	19
Gastric volume (mL/kg;	0.30	0.57*	0.54
mean ± SD)	±0.20	±0.39	±0.45
Patients with pH < 2.5			
Number	12	13	18
Percent	75	72	95
Patients with pH > 2.5			
Number	1	2	1
Percent	6	11	5
Dry cases, no pH measured			
Number	3	3	0
Percent	19	17	0
Safe cases			
Number	4	5	1
Percent	25	28	5

$*P < 0.05$ Kruskal-Wallis ANOVA with Dunn's multiple comparison when compared to group A.

5) and exhibited a significant decrease over time, $P < 0.001$, test for linear trends over time. Patients receiving no premedication (group A) also had a decrease in respiratory rate over time, $P = 0.024$, test for linear trends over time.

Mean and lowest oxygen saturations were not significantly different among the groups at all times. One patient in the placebo group had O_2 saturations less than 90% at 20, 50, and 60 min after baseline, and one patient receiving OTFC had O_2 saturations of 86% and 84% at 30 and 40 min after baseline. Both patients' oxygen saturation increased to >90% with the command to take a deep breath.

Table 5. Incidence (Percentage of Side Effects in Children Receiving No Premedication, Oral Transmucosal Fentanyl Citrate (OTFC) or a Placebo Lollipop for Premedication

	Group A No premed	Group B OTFC	Group C Placebo
N	18	18	19
Preoperative holding			
pruritus	0	50*	0
nausea	0	0	0
vomiting	0	0	0
Recovery room			
pruritus	0	6	0
nausea	0	44†	16
vomiting	17	22	16
After discharge from the recovery room			
pruritus	0	0	0
nausea	0	0	0
vomiting	0	6	0

$*P < 0.001$, χ^2, when compared to group A or group C.
$+P < 0.01$, χ^2, when compared to group A.

Patients in the three groups had similar awakening, first response to command, and discharge times in the recovery room and similar emergence scores. Five patients each in groups A and C and two in group B required narcotics in the recovery room. The differences between the groups were not statistically significant.

Facial pruritus occurred in 50% of the patients receiving OTFC with 15 occurrences in the preoperative holding area and one in the recovery room (Table 5). Facial pruritus did not occur in patients in groups A and C. Nausea and vomiting did not occur in any patient in the holding area or in the operating room. Nausea occurred in 16% and 44% of patients in C and B, respectively, but in no patients in group A in

the recovery room. The difference between groups A and B was statistically significant. Postoperative vomiting occurred in all three groups with equal frequency (Table 5). No other complications were noted.

Discussion

A number of studies have demonstrated that a high percentage of children have gastric volumes >0.4 mL/kg and gastric pH's <2.5 immediately before operation irrespective of premedication with a variety of classes and combinations of sedatives/hypnotics or no premedication (4–6). By definition these patients are at risk for acid aspiration. Salem et al. (4) showed that the gastric volumes of 206 pediatric patients averaged 0.60 mL/kg after no premedication and between means of 0.45 and 0.51 mL/kg after premedication with pentobarbital and combinations of morphine, atropine, or scopolamine given intramuscularly. Only after glycopyrrolate was added to the other premedicants was the ratio reduced to 0.18 mL/kg. Lundgren and coworkers (5) found that gastric volumes averaged as much as 0.8 mL/kg after premedication with flunitrazepam and between 0.4 to 0.45 mL/kg with diazepam, meperidine, and triclofos in children 5 years and older. These studies also showed that a low percentage of children can be classified as "dry cases" or "safe cases," as we found in all of our groups. Asking children to suck on a lollipop prior to induction of anesthesia only increases the potential problem of acid aspiration. We had hoped that the increased sedation and anxiolysis produced by OTFC might decrease gastric volume and increase gastric pH. Unfortunately, gastric volumes were increased in both groups that consumed lollipops, and gastric pH's were similar in all three groups. Perhaps gastric volumes might have been lower and gastric pH's higher if OTFC had been administered earlier (a longer period) before operation. However, this would not be practical in a modern operating room focused on rapid turnover of patients.

Although both OTFC and the placebo lollipop groups had significant increases in gastric volume (means of 7.6, 14.6, and 15.6 mL in groups A, B, and C, respectively) and gastric vol/kg ratios (means of 0.30, 0.57, and 0.54 mL/kg in groups A, B, and C, respectively) the increases were small (7 to 8 mL). Furthermore, the gastric volumes and pH's were still within the range of those found after no premedication or premedication with a variety of sedative/hypnotics (4–6) and the number and percent of patients having gastric pH's >2.5 or recorded as dry or

safe cases was similar after OTFC and no premedication. Finally, our results do not confirm that the increase in gastric volume after sucking on a lollipop increases preoperative, intraoperative, or postoperative vomiting. However, the low incidence of postoperative vomiting may have been affected by the stomach aspiration after tracheal intubation. Other studies have shown increases in postoperative vomiting after OTFC when gastric aspiration was not performed (3).

OTFC caused pruritus in approximately 50% to 80% of children in the preoperative holding area and less frequently after operation. It was difficult to differentiate pruritus from the eye- and nose-rubbing that occurs when children are sleepy and about to fall asleep. In this study any eye- or nose-rubbing was considered pruritus. Consequently, the incidence of pruritus is probably overestimated. Pruritus was rarely disturbing to patients or their parents and usually heralded the onset of sedation.

The only other potential concern after OTFC premedication is respiratory depression. Our study and those of others have found that the small decrease in respiratory rate is associated with a decrease in pulse oximeter measured oxygen saturation in about 5–7% of patients. In this study oxygenation saturation decreased to less than 90% in only one patient receiving OTFC and was easily corrected by asking the child to take a deep breath. Doses of OTFC >20 μg/kg do cause more respiratory depression (and more sedation) and should not be administered unless an anesthesiologist is continually present. To our knowledge an oxygen saturation <90% has never occurred in a child receiving OTFC in a dose <15 μg/kg.

Significant decreases in activity (increases in sedation) occurred in 10 min, and significant decreases in anxiety occurred 20 min after beginning OTFC. Yet, recovery room stays were not delayed in this study or others (3). We believe the reason for this is related to rapid penetration of fentanyl through oral mucus membranes and into vessels perfusing these tissues. Following consumption of OTFC, plasma fentanyl concentrations decrease rapidly (1).

The study was only partially double-blinded (investigators performing holding-room evaluations knew group A patients were a control group who received no premedication), because sedation and anxioloysis (requiring investigator evaluation) began before patients in groups B and C finished their lollipops. At all other periods during the study investigators were unaware of patient group allocation. In spite of incomplete double-blinding, we believe that the preoperative behavioral data are valuable because the patients were unaware of their group allocations,

and the scoring schedules used reasonably objective endpoints.

In conclusion, OTFC was readily accepted and safe, and provided increased sedation and less anxiety than patients having a placebo lollipop or no premedication between 10 and 20 min after beginning consumption. OTFC slightly increased gastric volume (when compared with patients having no premedication) but did not influence gastric juice pH, the percent of patients having gastric pH's above or below 2.5, or the number or percent of cases classified as "dry" or "safe." OTFC premedication also did not delay recovery or increase the incidence of vomiting, although it did cause preanesthetic pruritus (50%) and an increased incidence of postoperative nausea. The results suggest that OTFC deserves additional evaluation and comparison to more common drugs and methods of premedication in children.

References

1. Stanley TH, Hague BH, Mock DL, Streisand JB, Bubbers S, Dzelzkalns RR, Bailey PL, Pace NL, East KA, Ashburn MA. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anesth Analg 69:21–7.
2. Streisand JB, Stanley TH, Hague B, van Vreeswijk H, Ho GH, Pace NL. Oral transmucosal fentanyl citrate premedication in children. Anesth Analg 69:28–34.
3. Nelson P, Streisand JB, Mulder S, Pace NL, Stanley TH. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine. Anesthesiology 1989;70:616–21.
4. Salem MR, Wong AY, Mani M, Bennett EJ, Toyama T. Premedicant drugs and gastric juice pH and volume in pediatric patients. Anesthesiology 1976;44:216–9.
5. Lindgren L, Saarnivaara L, Himberg J-J. Comparison of oral triclofos, diazepam and flunitrazepam as premedicants in children undergoing otolaryngological surgery. Br J Anaesth 1980; 52:283–9.
6. Manchikanti L, Roush JR. Effect of preanaesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume in outpatients. Anesth Analg 1984;63:40–6.
7. Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 1970;49:924–34.

A Cost/Benefit Analysis of Randomized Invasive Monitoring for Patients Undergoing Cardiac Surgery

Kent S. Pearson, MD, Mark N. Gomez, MD, John R. Moyers, MD, James G. Carter, MD, and John H. Tinker, MD

PEARSON KS, GOMEZ MN, MOYERS JR, CARTER JG, TINKER JH. A cost/benefit analysis of randomized invasive monitoring for patients undergoing cardiac surgery. Anesth Analg 1989;69:336-41.

The aim of this study was to determine the effect of choice of invasive monitoring on cost, morbidity, and mortality in cardiac surgery. Two hundred and twenty-six adults undergoing elective cardiac surgery were initially assigned at random to receive either a central venous pressure monitoring catheter (group I), a conventional pulmonary artery (PA) catheter (group II), or a mixed venous oxygen saturation ($S\bar{v}_{O_2}$) measuring PA catheter (group III). If the attending anesthesiologist believed that the patient initially randomized to group I should have a PA catheter, that patient was then reassigned to receive either a conventional PA catheter (group IV) or $S\bar{v}_{O_2}$ measuring PA catheter (group V). The total costs were defined as the total amount billed to the patient for the catheter used; the professional cost of its insertion; and the determinations of cardiac output, arterial blood gas tensions, hemoglobin level, and

hematocrit. Mean total monitoring and laboratory costs in Group I ($591 ± 67) were statistically significantly (P < 0.05) less than costs in Group II ($856 = 231). Further, mean monitoring and laboratory costs in Group II were statistically significantly (P < 0.05) less than those in Group III ($1128 ± 759). Patients in group IV incurred mean total costs of $986 ± 578, while those in group V had mean total costs of $1126 ± 382 (NS). There were no significant differences between any of the groups with respect to length of stay in the intensive care unit, morbidity, or mortality. We conclude that use of a central venous pressure monitoring catheter was justified in low risk cardiac surgical patients, and that when PA catheters were used, additional costs were incurred. Additionally, monitoring of $S\bar{v}_{O_2}$ adds significant cost to that incurred with routine PA catheter use, but produces no discernible difference in patient outcome.

Key Words: ANESTHESIA, CARDIOVASCULAR—costs. MONITORING, COSTS—cardiac surgery. ECONOMICS, COSTS OF MONITORING.

Either pulmonary artery (PA) or central venous catheters are widely used monitors during and immediately after cardiac surgery. Whether use of a PA catheter as opposed to a central venous catheter is actually associated with decreased morbidity or mortality in such patients remains a subject of controversy. The greater cost of the PA catheter suggests that the cost/benefit ratio of monitoring devices for patients undergoing cardiac surgery should be evaluated. Addition of fiberoptic infrared mixed venous oxygen saturation ($S\bar{v}_{O_2}$) measurement capability to PA catheters provides still more information, but at even greater cost. Mixed venous oxygen saturation reflects oxygen delivery, oxygen consumption, cardiac output, and hemoglobin concentration (1). It has been contended that such continuous monitoring of mixed venous oxygen saturation reduces the frequency of measurements of cardiac output and arterial blood gas tensions, and that such reductions offset the increased catheter costs, possibly even reducing total patient monitoring costs (2).

Accordingly, we performed a prospective randomized study in 226 cardiac surgical patients, designed to answer the following questions:

1. Is the use of PA catheters, with or without continuous measurement of $S\bar{v}_{O_2}$, associated with decreased morbidity, mortality, or costs compared with use of central venous pressure monitors?
2. Is the addition of continuous $S\bar{v}_{O_2}$ monitoring associated with reduced morbidity, mortality, or

cost below that incurred with use of standard PA catheters?

3. Does continuous $S\bar{v}_{O_2}$ monitoring reduce the cost or need for measurements of arterial blood gas tensions and cardiac outputs?

Materials and Methods

Following Human Studies Review Committee approval, 226 adults consecutively scheduled for elective cardiac surgery over a 9-month period were prospectively randomized prior to anesthesia and surgery to receive one of the following monitoring catheters: group I, central venous catheter (Arrow sheath introducer); group II, PA catheter (Edwards 7.5 Fr. VIP Swan Ganz catheter), group III, fiberoptic infrared mixed venous oxygen measuring PA catheter (Oximetrix 7.5 Fr.). Using a table of random numbers, each patient was assigned to one of the above groups. Ethical considerations led to some rerandomization of group I patients. If in the judgment of the attending anesthesiologist a PA catheter was indicated for a patient initially randomized to group I, that patient was then reassigned to receive either a standard PA catheter, group IV, or an $S\bar{v}_{O_2}$ measuring pulmonary artery catheter, group V. This reassignment was based on patient hospital number, as follows: if the last digit of the patient identification number was even, that patient was reassigned to receive a standard PA catheter; if the last digit was odd, that patient was reassigned to receive an $S\bar{v}_{O_2}$ measuring PA catheter. All patients had left atrial catheters inserted intraoperatively by the surgeon.

Data were collected on costs of the catheters used, plus postoperative intensive care and monitoring costs. The costs billed to each patient included the cost of the monitoring catheter selected, costs charged by the physician for catheter insertion, and costs for measurements of arterial blood gas tensions, cardiac output, hemoglobin, and hematocrit. The costs of the catheter and its insertion were incurred only once for each patient and were determined before the beginning of the study. While the costs of single measurements of arterial blood gas tension, cardiac output, hemoglobin, or hematocrit were also fixed, the number of determinations of each of these tests for each patient was variable and accounted for some of the differences in total costs among patients. Group I patients, of course, had no costs for cardiac output measurement. Additionally, length of intensive care unit (ICU) stay and total hours of inotrope and vasodilator therapy were recorded.

Upon admission to the ICU, all patients routinely had a battery of laboratory measurements that in-cluded hemoglobin, hematocrit, and arterial blood gas tensions. Following these initial laboratory determinations, all further laboratory tests were obtained because of changes in patient status, e.g., arterial blood gas determinations during weaning from mechanical ventilation. Patients with PA catheters had cardiac output determinations carried out to diagnose changes in clinical condition, or to follow changes in status associated with changes in management. Vasodilators were administered to control hypertension, generally systolic blood pressure greater than 140 mm Hg. Inotropic agents were used as treatment of hypotension defined as systolic blood pressure of less than 100 mm Hg. Combinations of inotropic agents and vasodilators were used for treatment of persistent low cardiac output, diagnosed by either a cardiac index of less than 2.5 L/min/m^2, or by clinical findings of oliguria, poor peripheral perfusion, and hypotension.

Before the start of our study, intensive care unit nurses and housestaff physicians underwent specific in-service training in $S\bar{v}_{O_2}$ monitoring given by intensive care physicians and representatives of the catheter manufacturer. They were deliberately not informed that a purpose of our study was cost/benefit analysis, but were rather encouraged to utilize the information provided by the $S\bar{v}_{O_2}$ monitoring to reduce the number of cardiac output and laboratory determinations. Differences in results between groups were assessed by two-way analysis of variance (ANOVA). Post-ANOVA multiple comparisons were performed using Kruskal-Wallis nonparametric analysis of variance, with frequency comparisons performed using the distribution-free multiple comparison test (3). Values of $P < 0.05$ were considered statistically significant. Unless otherwise noted, all values are expressed as mean ± standard deviation (mean ± SD).

Results

Patient data on surgical procedure, left ventricular ejection fraction, and ICU stay are presented in Table 1. Of the 74 patients initially randomized to group I (central venous pressure [CVP] monitoring), 33 were reassigned to group IV (PA catheter monitoring), and 13 were reassigned to group V ($S\bar{v}_{O_2}$ monitoring). This reassignment was based on the patient's hospital number, not on a new random number assignment, which led to the uneven distribution of patients into groups IV and V. All patients received high-dose narcotic anesthesia with 50–100 μg/kg fentanyl, with muscle relaxation maintained with either

Table 1. Data for Surgical Procedure, Preoperative Left Ventricular Ejection Fraction and Intensive Care Unit Stay

Group	CABG	Valve	CABG+Valve	LVEF (Mean + SD)	Days in ICU (Mean + SD)	Median Number of ICU days
I 28	26 (93%)*	0†	2 (7%)	64 ± 9%	1.35 ± 1.1	1.0
II 86	62 (72%)	14 (16%)	10 (12%)	52 ± 14%	1.6 ± 1.1	1.0
III 66	48 (73%)	12 (18%)	6 (9%)	55 ± 19%	2.1 ± 4.1	1.0
IV 33	23 (70%)	7 (21%)	3 (9%)	47 ± 16%‡	2.8 ± 5.0	1.0
V 13	9 (69%)	3 (23%)	1 (8%)	58 ± 13%	2.6 ± 3.8	1.0

CABG = coronary artery bypass grafting, Valve = cardiac valvular surgery, CABG+valve = combined coronary artery bypass grafting and cardiac valvular surgery, LVEF = left ventricular ejection fraction, and ICU = Intensive Care Unit.
*significantly more than other groups.
†significantly fewer than other groups.
‡significantly lower than group I.

Table 2. Duration of Administration of Vasoactive Drugs Postoperatively

Group	Hr of Vasodilator use (mean ± SD)	Range (hr)
I	7.92 ± 7.69	0–24
II	10.70 ± 10.39	0–50
III	17.43 ± 39.52	0–303
IV	22.36 ± 54.90	0–312
V	10.84 ± 8.81	0–11

Group	Hr of Vasopressor use (mean ± SD)	Range (hr)
I	2.14 ± 5.08	0–21
II	5.88 ± 9.81	0–49
III	9.92 ± 34.64	0–255
IV	8.21 ± 19.96	0–90
V	6.30 ± 3.25	0–36

pancuronium or vecuronium. In the intensive care unit, morphine was administered as required for pain, and diazepam or midazolam was administered as required for sedation. Patients were weaned from mechanical ventilation and extubated when awake and hemodynamically stable.

The mean left ventricular ejection fraction (LVEF) of patients in group I was significantly greater than in group IV patients (Table 1). More patients had coronary artery bypass grafting and fewer had valvular surgery in group I compared to all other groups. There were no significant differences among any of the groups in length of ICU stay (Table 1).

Duration of administration of vasoactive drug infusions postoperatively, in hours, is shown in Table 2. The vasodilators used were nitroglycerin and nitroprusside. There were no statistically significant differences among groups in duration of vasodilator administration. The vasopressors used were epinephrine and dopamine. Again, there was no statistically significant difference among groups in duration of administration of vasopressors (Table 2).

Costs for insertion plus costs of catheters for all patients in group I were $388; for all patients in both

groups II and IV were $415; and for all patients in groups III and V were $551. Total costs and costs for cardiac outputs and laboratory measurements associated with the use of the three catheters are displayed in Table 3. These included costs of the monitoring catheter selected, professional insertion, and the measurements of arterial blood gas tensions, cardiac output determinations, hemoglobin levels, and hematocrits. There was no statistically significant difference between groups in costs of arterial blood gas tension determinations or costs of hemoglobin levels or hematocrits (Table 3). No statistically significant differences between the groups receiving either type of PA catheter were noted for costs of cardiac output determinations (Table 3). Total monitoring and laboratory costs averaged $591.19 ± 68 in group I, $855.51 ± 231 in group II, and $1128.38 ± 759 in group III. Among the patients who had the catheter as originally intended after randomization, there were statistically significant higher costs between groups I, II, and III, with each group incurring greater costs than the prior group. The patients who were reassigned from group I (CVP) to either PA catheter group had a mean total cost of $986.38 ± 578 in group IV and $1126.38 ± 382 in group V. This cost difference did not reach statistical significance. The costs in both groups IV and V were statistically significantly greater than the costs in group I. There were no intraoperative deaths in patients in this study. There were no deaths in the ICU among patients in groups I, II, or V. One patient in group III and one patient in group IV died in the ICU. The death rates were not significantly different among groups.

Discussion

We used the term "costs" throughout our report to refer to the dollar amount billed to the patient. Some would prefer to use "charges" or "fees" for this data, because "costs" are sometimes used to refer to actual

Table 3. Costs Related to Each Type of Monitoring
Catheter Used

Costs of Arterial Blood Gas (ABG) Measurement (Mean ± SD)	Median ABG Costs	Range ABG Costs
I $187.50 ± 105	$170.62	$68.25–250.25
II $212.32 ± 102	$185.50	$68.25–568.75
III $231.42 ± 257	$182.00	$68.25–2070.25
IV $283.40 ± 248	$204.75	$68.25–1319.50
V $260.75 ± 228	$182.00	$68.25–932.75

Costs of Cardiac Output (C.O.) Measurements (Mean ± SD)	Median C.O. Costs	Range C.O. Costs
I 0	0	0
II $191.88 ± 151.14	$151.00	$0–830.50
III $282.93 ± 482	$151.00	$0–3020.00
IV $258.28 ± 375	$151.00	$0–1963.00
V $554.80 ± 1205	$226.50	$0–4539.00

Costs for Measurement of Hemoglobin and Hematocrit (Hb & Hct) (Mean ± SD)	Median Hb & Hct Costs	Range Hb & Hct Costs
I $26.25 ± 21	$21.00	$14.00–91.00
II $34.45 ± 47	$28.00	$7.00–450.00
III $32.77 ± 33	$21.00	$14.00–224.00
IV $34.36 ± 21	$28.00	$14.00–119.00
V $36.07 ± 32	$28.00	$7.00–112.00

Total Costs (Mean ± SD)	Median Total Costs	Range Total Costs
I $591.19 ± 68*	$387.19	$500.06–864.50
II $855.51 ± 231†	$811.78	$504.40–1861.90
III $1128.38 ± 759	$938.06	$701.31–5978.56
IV $986.38 ± 578†	$776.40	$572.90–2896.40
V $1126.38 ± 382	$1002.81	$738.06–2162.06

Total costs include catheter, insertion cost, cardiac output measurement and laboratory costs.
*significantly less than groups II–V.
†significantly less than group III.

costs to the hospital for supplies. Services by hospitals are often referred to as "charges," whereas services rendered by physicians are often called "fees." Patients are usually charged more than the hospital's actual cost for a given supply item. We attempted to perform a "cost"/benefit analysis and thus were confronted with the necessity of deciding among the use of the hospital's actual cost for supply items, the physician's fees charged to the patient, and either the laboratory services' actual costs or their charges to the patients. The actual "cost" of physician services is yet another amount, one probably impossible to determine. We decided that for this study, "cost" meant the dollar amount actually billed to the patient, whether for supplies, hospital laboratory services, or professional services. We think this pro-

duced the most consistent way to compare these three methods of monitoring.

Those patients who remained in group I and were thus monitored throughout the perioperative period with central venous catheters had the lowest total costs in the study. This was due to lower catheter-related costs and to the fact that there were no costs for measurements of cardiac outputs. Whether or not this was a less seriously ill group of patients, there were statistically significant mean savings of over $250 per patient compared to group II, and over $530 per patient compared to group III. This was not associated with increased morbidity or mortality. We believe our results to be in agreement with those reported by Bashein et al. (3). Their retrospective study of 698 patients concluded that patients with good left ventricular ejection fraction and no history of congestive heart failure could safely undergo coronary artery bypass grafting without use of a PA catheter. In our study, in 64.5% of the patients initially randomized to group I, the clinicians considered that a PA catheter was necessary rather than a CVP catheter alone, and therefore these patients were reassigned to one of the two PA catheter groups. Decisions to reassign were based on severity of cardiac disease and followed published recommendations (5–7), but no attempt was made to control these decisions, since the decisions themselves were "outcome" data and provided numerical evidence of the frequency with which such decisions did occur, at least in our practice. All patients had left atrial catheters placed after sternotomy, though these were removed early in the postoperative period.

The patients randomized to group II, the "standard" PA catheter group, incurred intermediate total costs (Table 3) significantly greater than the costs associated with the CVP group, but significantly less than the costs associated with the $S\bar{v}_{O_2}$ catheter group. The higher costs in group II were due to the increased cost of the catheter itself, cost for insertion, and costs for cardiac output determinations.

Patients in group III, the $S\bar{v}_{O_2}$ PA catheter group, had the highest costs in our study. The cost of the catheter itself was $135.00 more than the cost of a conventional PA catheter. Despite the contention that $S\bar{v}_{O_2}$ monitoring should lead to fewer cardiac output determinations, the patients in group III had higher average costs for cardiac output determinations ($282.23 vs $191.88) than those in group II, although this difference did not reach statistical significance. The result was a significant increase in mean total cost of $272.87 per patient for mixed venous oxygen saturation monitoring in patients in group III, compared to those in group II. Clearly, the notion that

$S\bar{v}_{O_2}$ monitoring, even with "in-service" training, would lower perceived needs for cardiac output determinations was not the case in our study. This study was begun 9 months after the introduction of $S\bar{v}_{O_2}$ monitoring catheters into our intensive care unit. We believe that this 9 months was an adequate amount of time for faculty and housestaff to gain familiarity and confidence in the use of mixed venous oxygen saturation monitors before the start of our data collection. There was no difference between the mean cost for the first ten patients who had $S\bar{v}_{O_2}$ monitoring and for the last ten patients: $950.64 vs $997.23, respectively, reflecting no "learning curve."

Results from patients rerandomized from group I to either group IV or V were somewhat different. Again, costs for these patients were significantly higher than in patients monitored with CVP catheters alone, but the difference in costs between groups IV and V did not reach statistical significance, probably due to the small size of group V. In contrast, the difference in costs between group IV (reassigned conventional PA) and group III ($S\bar{v}_{O_2}$ monitoring catheter) patients did achieve statistical significance. It must be noted that patients in both groups IV and V were chosen for these groups based on the clinician's judgment that they represented a higher risk group and would benefit from PA catheter monitoring.

At our institution, patients with a PA catheter in place are not charged any daily PA "monitoring" costs, as is the case in many other hospitals, but instead are charged for individual output cardiac determinations. We reported the actual dollar amounts billed to our patients. Obviously, our data represents only the costs at our hospital. It must also be emphasized that there were no differences between groups with PA monitors in costs of cardiac output measurements; therefore, the total costs of cardiac output determinations did not confound the results.

Differences between patients in our five groups of patients included the fact that patients remaining in group I had significantly higher LV ejection fractions than patients in group IV. Also, a smaller percentage of patients in group I underwent valve replacements and combined coronary artery grafts and valve replacements than did those in the other groups. We could, however, detect no differences in severity of illness between patients in groups II through V. The patients in groups II through V had similar ejection fractions and had no significant differences in the types of operations performed. Further, there were no differences in mortality rates, pressor or vasodilator requirements, or durations of stay in the ICU between these groups. Our data lead us to reject the hypothesis that continuous $S\bar{v}_{O_2}$ monitoring reduces

either need or costs of postoperative arterial blood gas and cardiac output determinations in postcardiac surgical patients. We found neither morbidity nor mortality-related reasons to justify the 25% additional average cost of $S\bar{v}_{O_2}$ monitoring over that for the conventional PA catheters. L. O. Larson and J. V. Kyff (Department of Anesthesiology, University of Michigan, personal communication, January 1988) in a retrospective study of 87 patients undergoing coronary artery bypass grafting also found no differences in morbidity or mortality or ICU stay attributable to use of an $S\bar{v}_{O_2}$ measuring PA catheter.

In contrast, Orlando stated that $S\bar{v}_{O_2}$ monitoring eliminated the need for an average of 5.9 venous blood gas determinations and 2.65 cardiac output measurements per patient studied. This resulted in net savings of $75.00 per patient with use of $S\bar{v}_{O_2}$ monitoring (8). This study had no "control" group of patients receiving standard PA catheters without $S\bar{v}_{O_2}$ measuring capability but rather relied on recording all instances in which, in the judgment of the investigator, the need for venous blood gas sampling or measurement of cardiac output was eliminated by continuous venous oximetry. His study of 20 patients included only three postoperative cardiac surgical patients. Perhaps the differences in results between our study and Orlando's were due to the large proportion of noncardiac surgical patients in his series, differences in postoperative management in the intensive care unit, or sampling of venous rather than arterial blood. Schweiss stated that when $S\bar{v}_{O_2}$-measuring catheters were used, the increased cost for the monitoring catheters was less than 15% above that for conventional PA catheters, and improved patient care (9). In contrast, we found the cost of $S\bar{v}_{O_2}$ monitoring to be 25% more than conventional PA monitoring, and we could document no improvement in outcome in a considerably larger series of prospectively studied patients. Schweiss did not provide outcome data to substantiate his contention that patient care was improved, nor did he include a concurrent control group for comparison of monitoring techniques.

The clinical utility of mixed venous saturation measurement must be considered. We found no differences in morbidity, mortality, or outcome between the two PA catheter groups. Boutros and Lee failed to detect differences in patient management due to $S\bar{v}_{O_2}$ monitoring in a group of 15 critically ill patients (10). Watson et al., in an editorial and review of the literature, concluded that $S\bar{v}_{O_2}$ measurement may lack specificity, and that merely following $S\bar{v}_{O_2}$ trends could lead to inappropriate therapeutic interventions (11). Magilligan et al. found mixed venous

oxygen saturations to be poor predictors of cardiac index in postoperative cardiac surgical patients, and also that $S\bar{v}_{O_2}$ did not reliably predict cardiac indices of less than 2.0 L/min/m² (12). With respect to the rapid changes in oxygen utilization that occur beginning with rewarming, continuing with intraoperative termination of extracorporeal circulation, and also into the postoperative period, it is not surprising to us that few therapeutic decisions were based only on $S\bar{v}_{O_2}$ levels.

In conclusion, we found that patients with good cardiac function could safely undergo cardiac surgery with monitoring of only CVP and left atrial pressure at considerably reduced cost. We cannot conclude that all patients would have done equally well with CVP monitoring alone, and in fact the attending anesthesiologist's decision to take some patients out of the randomly assigned CVP group might have contributed to the lack of differences between groups in morbidity and mortality. Neither cost, mortality, nor morbidity were reduced in patients requiring PA catheters for cardiac surgery when $S\bar{v}_{O_2}$ monitoring capability was added. Indeed, we found costs associated with $S\bar{v}_{O_2}$ monitoring catheters to be considerably higher, despite a deliberate reverse bias introduced by in-service training.

References

1. McMichan JL. Continuous monitoring of mixed venous oxygen saturation in clinical practice. Mt Sinai J Med (NY) 1984; 51:569–72.

2. Aberman A. Fundamentals of oxygen transport physiology in a hemodynamic monitoring context. In: Schweiss, JF, ed. Continuous Measurement of Blood Oxygen Saturation in the High Risk Patient, Vol. 1. San Diego: Beach International, 1983:13–26.

3. Hollander M, Wolfe D: Nonparametric Statistical Methods. New York: John Wiley and Sons, 1973:124–5.

4. Bashein G, Johnson AW, Davis KB, Ivey TD. Elective coronary bypass surgery without pulmonary artery catheter monitoring. Anesthesiology 1985;63:451–6.

5. Kaplan JA. Hemodynamic monitoring. In: Kaplan JA, ed. Cardiac Anesthesia, 2nd ed. Orlando: Grune and Stratton, 1987:179–226.

6. Ream AK. Monitoring concepts and techniques. In: Ream AK, Fogdall RP, eds. Acute Cardiovascular Management: Anesthesia and Intensive Care. Philadelphia: JB Lippincott, 1982: 139–60.

7. Barash PG, Kopriva CS. Cardiac pump function and how to monitor it. In: Thomas SJ, ed. Manual of Cardiac Anesthesia. New York: Churchill Livingstone, 1984:1–34.

8. Orlando R. Continuous mixed venous oximetry in critically ill surgical patients. Arch Surg 1986;121:470–71.

9. Schweiss JF. Mixed venous oxygen saturation: theory and application. In: Tremper KK, Barker SJ, eds. Advances in Oxygen Monitoring. Int Anesthesiol Clin 1987;25:113–36.

10. Boutros AR, Lee C. Value of continuous monitoring of mixed venous blood oxygen saturation in the management of critically ill patients. Crit Care Med 1985;14:132–4.

11. Waston CB: Continuous measurement of mixed venous oxygen saturation: shall we worship the golden calf? J Clin Monit 1985;1:252–8.

12. Magilligan DJ, Teasdall R, Kisinminger R, Petersen E. Mixed venous oxygen saturation as a predictor of cardiac output in the postoperative cardiac surgical patient. Ann Thorac Surg 1987;44:260–2.

Time-Courses of Zones of Differential Sensory Blockade during Spinal Anesthesia with Hyperbaric Tetracaine or Bupivacaine

Sorin J. Brull, MD and Nicholas M. Greene, MD

BRULL SJ, GREENE NM. Time-courses of zones of differential sensory blockade during spinal anesthesia with hyperbaric tetracaine or bupivacaine. Anesth Analg 1989;69:342-7.

The purposes of this study were twofold: to compare bupivacaine and tetracaine spinal anesthesia with regard to the zones of differential sensory blockade and to evaluate the time-courses of the widths of the zones of differential sensory blockade during spinal anesthesia. In 51 patients, the most rostral levels of sensory denervation to light touch, pinprick, and temperature discrimination were measured. There was no statistically significant difference in the height of sensory blockade in the 29 patients given bupivacaine and in the 22 patients given equipotent doses of tetracaine. The widths of the zones of differential blockade were also not statistically different between the two groups during onset, maintenance, and regression of anesthesia, except that the

light touch-to-pinprick and light touch-to-temperature zones of differential blockade were greater with bupivacaine than with tetracaine 30 min after subarachnoid injection. The width of the zones of differential blockade also remained unchanged within each group during onset, maintenance, and regression of anesthesia. Changes in, and absolute levels of, blood pressure and heart rate were similar with both bupivacaine and tetracaine throughout. We conclude that zones of differential sensory blockade are essentially the same with tetracaine and bupivacaine, that the widths of the zones of differential sensory blockade remain constant during onset, maintenance, and offset of spinal anesthesia, and that bupivacaine and tetracaine are associated with similar changes in heart rate and blood pressure during spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES, SPINAL. ANESTHETICS, LOCAL—bupivacaine, tetracaine.

Spinal anesthesia is associated with zones of differential nerve blockade (1). Bupivacaine and tetracaine, long-acting local anesthetics commonly used for spinal anesthesia, have not been compared with regard to the zones of differential blockade to light touch, pinprick, and temperature discrimination. These zones of differential blockade contribute to determining physiologic responses to spinal anesthesia, especially cardiovascular changes. Whether equal sensory levels of hyperbaric bupivacaine and hyperbaric tetracaine are associated with similar changes in blood pressure and heart rate during spinal anesthesia is controversial. Any difference might be due to a less extensive sympathetic denervation with one local anesthetic than with the other, despite equal sensory levels. This may occur inasmuch as there is also a zone of differential blockade involving preganglionic

sympathetic fibers during spinal anesthesia, and because the degree of sympathetic denervation is a major determinant of cardiovascular changes during spinal anesthesia.

We undertook a prospective, single-blind study to define the magnitude, duration, and extent of zones of differential blockade during hyperbaric tetracaine and bupivacaine spinal anesthetics, and to define the relation of the zones of differential blockade to changes in blood pressure and heart rate.

Methods

Fifty-one patients scheduled for spinal anesthesia for elective surgery were assigned to receive hyperbaric bupivacaine (0.75% in 8.25% dextrose) or hyperbaric tetracaine (0.5% in 5% dextrose). Criteria for inclusion in this institutionally approved study were: 1) patients' ability to speak and understand English; 2) their ability to understand and give consent to the proposed study; 3) age of 18–80 years; 4) operations in which spinal anesthesia was indicated; and 5)

absence of contraindications to spinal anesthesia. Patients were premedicated with a benzodiazepine (diazepam or midazolam) in amounts adequate to relieve anxiety without undue sedation. Intraoperatively, benzodiazepines were given intravenously in small, repeated doses as necessary to relieve anxiety without producing undue sedation. Preoperative and intraoperative narcotics were limited to a total of 2 μg/kg of fentanyl or its equivalent.

Intraoperatively, patients were monitored using prevailing departmental standards for patients undergoing spinal anesthesia. Choice and dose of anesthetic agent and technique were determined by the resident and the attending anesthesiologist assigned to provide the anesthetic care. Dural punctures were performed at the lumbar interspace of choice by the anesthesiologist, with patients in the position appropriate for the proposed surgery and, thus, for the level of desired sensory blockade.

All sensory responses were measured by the same anesthesiologist (Dr. Brull), who was blinded to the local anesthetic used for spinal anesthesia. This observer did not participate in the perioperative administration of intravenous fluids or medications, including drugs for treatment of intraoperative hypotension or bradycardia.

The dermatomal levels of blockade of light touch (LT), temperature (T), and pinprick (PP) discrimination, as well as blood pressure (BP) and heart rate (HR) were measured 5, 10, 15, and 30 min and thereafter every 30 min after intrathecal injection of the local anesthetic, until LT sensory level regressed to the T-12 dermatome using the dermatomal chart described by Bromage (2).

The most craniad extension of the loss of each sensory modality was determined by asking the patient to compare differences between sensory stimuli applied to an unanesthetized area (e.g., the shoulder tip) and to the trunk in the midclavicular line. The level caudad to the lowest dermatome at which the sensory stimulus felt the same as at the shoulder tip was considered the most cephalad level of blockade of the sensory modality being tested.

Light touch was measured by applying the dull, hinged end of a sterile safety pin to the skin without indenting it. Temperature was measured by spraying the skin with a nontoxic, nonflammable, highly volatile mixture of dichlorofluoromethane and trichloromonofluoromethane (Flouri-Methane, Gebauer). Pinprick was measured using the sharp tip of a sterile safety pin protruding 3 mm beyond a rubber stopper. Blood pressure was measured using an automated sphygmomanometer, and HR was determined by electrocardiogram (ECG).

Table 1. Patient Demographics

	Bupivacaine	Tetracaine
Age (yr)	64.8 ± 11.95	58.4 ± 13.83
Sex (M/F)	26/3	18/4
Height (cm)	175.9 ± 6.67	174.0 ± 8.72
Weight (kg)	76.3 ± 12.59	79.9 ± 17.46
Anesthetic dose (mg)	13.0 ± 2.14	12.4 ± 1.95
N	29	22

Values are means ± SD. No significant differences were noted between groups.
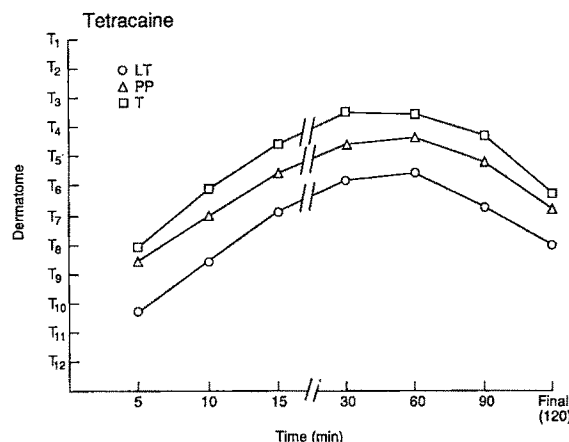
Figure 1. Level of thoracic dermatomal blockade of light touch (LT), pinprick (PP), and temperature (T) discrimination as a function of time (min), during tetracaine spinal anesthesia.

Data were analyzed as follows: 1) Continuous variables were analyzed using analysis of variance (ANOVA), with P values <0.05 considered statistically significant. 2) Discrete variables were analyzed using χ^2 tests, with P values <0.05 considered statistically significant. Data are presented as mean values ± SD.

Results

Of the 51 patients in this study, 29 were given bupivacaine and 22 tetracaine. The two groups were not statistically different with regard to sex, ASA physical status, age, weight, height, or dose (1 mg of bupivacaine in 8.25% dextrose and 1 mg of tetracaine in 10% dextrose being considered equipotent [3]) of local anesthetic used (Table 1).

Levels of loss of LT, PP, and T discrimination during tetracaine and bupivacaine spinal anesthesia are shown in Figures 1 and 2. The highest (most rostral) levels of sensory denervation in the tetracaine group included an LT sensory level at the thoracic 5.5 ± 1.99, a PP sensory level at the thoracic 4.1 ± 1.36, and a T sensory level at the thoracic 3.2 ± 1.72
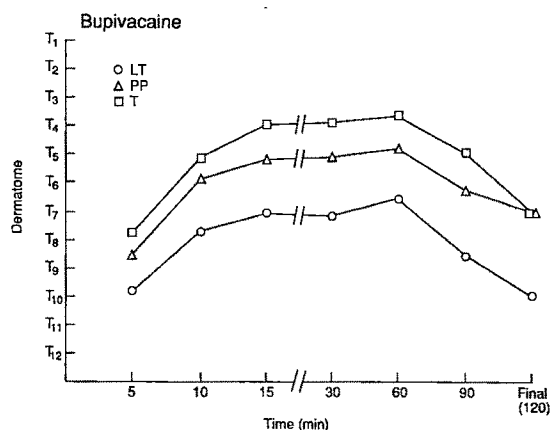
Figure 2. Level of thoracic dermatomal blockade of light touch (LT), pinprick (PP), and temperature (T) discrimination as a function of time (min) during bupivacaine spinal anesthesia.
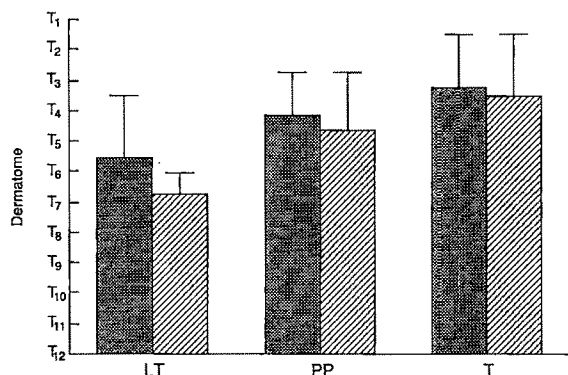
Figure 3. Most cephalad levels of blockade of light touch (LT), pinprick (PP), and temperature (T) discrimination during tetracaine (cross-hatched) and bupivacaine (diagonal lines) spinal anesthesia. Mean ± SD. No statistically significant difference was noted between the two local anesthetics.

Table 2. Width of Zones of Differential Blockade of Light Touch, Pinprick, and Temperature Discrimination during Bupivacaine and Tetracaine Spinal Anesthesia, as a Function of Time

	Time after Injection (minutes)						
	5	10	15	30	60	90	Final
LT-PP							
BU	1.54	1.76	1.86	2.07	2.09	2.89	3.00
TE	1.45	1.55	1.32	1.23 [a]	1.22	1.50	1.25
PP-T							
BU	0.79	0.79	1.14	1.24	1.17	1.30	0.00
TE	1.0	0.86	1.05	1.05	0.94	0.90	0.50
LT-T							
BU	2.38	2.55	3.00	3.31	3.18	4.00	3.00
TE	2.45	2.41	2.36	2.29 [a]	2.17	2.40	1.75

Abbreviations: BU, bupivacaine; LT-PP, light touch to pinprick; LT-T, light touch to temperature; PP-T, pinprick to temperature; TE, tetracaine.
[a] Statistically significant differences.
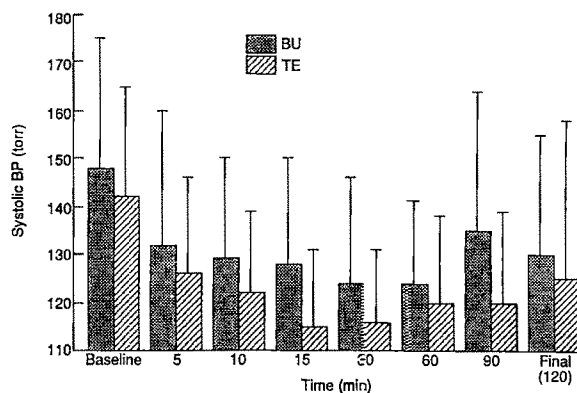
Figure 4. Systolic blood pressure (BP) measurement (torr) preoperatively (Baseline) and intraoperatively as a function of time (min) during tetracaine (cross-hatched) and bupivacaine (diagonal lines) spinal anesthesia. Mean ± SD. No statistically significant differences were noted between the two local anesthetics.

dermatomes (Figure 3). These levels of thoracic dermatomal denervation did not differ significantly from the highest levels of sensory denervation in the bupivacaine group, in which the LT level was at the thoracic 6.8 ± .71, PP at the thoracic 4.6 ± 1.85, and T at the thoracic 3.6 ± 2.04 levels (Figure 3).

The widths of the differential blockade zones (i.e., dermatomal differences of LT-PP, PP-T, and LT-T) were not statistically different between tetracaine and bupivacaine spinal anesthesia at any of the times evaluated, except that the widths of the LT-PP and LT-T zones of differential blockade at 30 min were greater with bupivacaine than with tetracaine (Table 2).

The widths of the zones of differential blockade showed no statistically significant change within either group during onset, maintenance, or regression of spinal anesthesia. The increase with time of the differential sensory block with bupivacaine (Figures 1

and 2) was not statistically significant. Levels of, and changes in, BP (Figure 4) and HR (Figure 5) were similar with both bupivacaine and tetracaine at all times.

Discussion

The present study confirms yet again the existence of zones of differential sensory blockade during spinal anesthesia. In 1950, Sinclair and Hinshaw (4) showed different sensitivities of mixed peripheral nerves to local anesthetics, with the relative order of sensory loss being cold first, then warmth, and then pain. In other studies, Sarnoff and Arrowood (5,6) observed increases in cutaneous temperature due to block of sympathetic fibers at doses of local anesthetic (procaine) that also blocked the sensation to pinprick but spared light touch and motor activity.
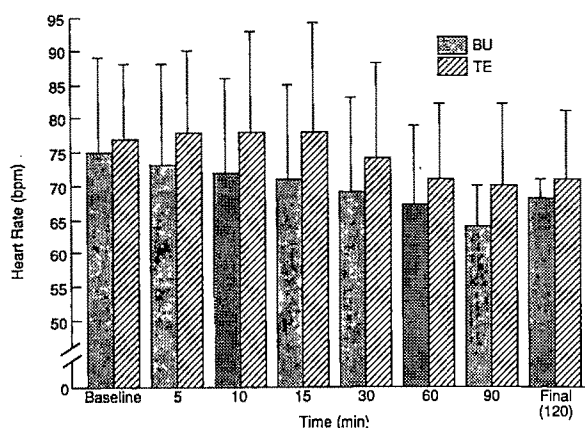
Figure 5. Heart rate (beats/min [*bpm*]) preoperatively (*Baseline*) and intraoperatively as a function of time (min) during tetracaine (*cross-hatched*) and bupivacaine (*diagonal lines*) spinal anesthesia. Mean ± SD. No statistically significant differences were noted between the two local anesthetics.

Greene (1), using cold sensation as an indication of probable sympathetic block, showed that the level at which temperature discrimination was lost averaged two spinal segments higher than the level made anesthetic to pinprick when hyperbaric tetracaine was used.

The etiology of the zones of differential blockade remains incompletely defined. When first reported in 1958 (1), it was suggested that the zones of differential blockade reflected, as suggested by Gasser and Erlanger (7) in 1929, differences in sensitivity of different types of nerve fibers to local anesthetics based on differences in nerve fiber size. The smaller nerves, according to this theory, were more sensitive to the effects of local anesthetics because of the greater membrane surface area per unit volume of axon in small fibers. The same mechanism for the differential sensory blockade had been proposed earlier by Helrich et al. (8) and Kitahara et al. (9), who showed that the concentration of a local anesthetic in the subarachnoid space decreased as the distance from the site of injection increased, different fibers thus being exposed to different concentrations of local anesthetic. These explanations were further refined by Hodgkin and Huxley (10), who postulated the existence of fast sodium channels involved in generation of an action potential. In the resting state, sodium channels respond to a suprathreshhold stimulus by opening and allowing an influx of sodium ions for a short period of time (0.4–0.6 msec). This sodium ion influx changes the resting membrane potential with generation of an action potential (depolarization). Local anesthetics are thought to act in part on specific receptors that control the opening and closing of the sodium channels, and by blocking

sodium conductance, they block the generation of action potentials (11).

In 1975, Courtney et al. (12,13) proposed that "frequency-dependent" or "use-dependent" conduction block explains why local anesthetics block trains of action potentials more effectively than they block single action-potentials. This frequency-dependent conduction block theory may also explain selective block of different sensory nerve types (differential sensory blockade): a phasic sensory nerve cell, which is firing short and widely separated bursts, is more resistant to local anesthetic blockade than a nerve cell which is firing long, continuous, and high-frequency bursts. The explanation for the greater ease of blockade of high-frequency, as opposed to phasic, action potentials, is that the sodium channels are in the open position a proportionally longer period of time, thus allowing the local anesthetics more time to act on the receptors and thus block the generation of high-frequency action potentials. Though the phenomenon of frequency-dependent conduction block may play an important role in modulating anesthetic-associated differential analgesia (13), there is still controversy as to the exact mechanism responsible for differential sensory blockade during spinal anesthesia, and the current study is not an attempt to resolve this dispute.

Current studies have compared the extent of somatic sensory blockade with different local anesthetics, but few have related the extent of sensory blockade to simultaneous measurement of sympathetic blockade. The former type of studies include that of Rocco et al. (14), who found greater maximal extent of sensory anesthesia to pinprick with bupivacaine, but longer total duration of sensory anesthesia with tetracaine, when equal doses (15 mg), concentrations (0.375%), volumes (4 mL), and glucose concentrations (5%) of solutions of tetracaine and bupivacaine were used. Rocco et al. (15), also in a study of differences in the degree of spread of sensory blockade to pinprick, cold, and touch, found that loss of touch perception was delayed, never extending as far cephalad as loss of temperature and pinprick discrimination, and regressed sooner with tetracaine than with bupivacaine spinal anesthesia. Neither of these studies (14,15) attempted to correlate the extent of zones of sensory denervation with changes in heart rate or blood pressure, unlike the present study.

With regard to differences in levels of sympathetic blockade and changes in blood pressure and heart rate seen with hyperbaric bupivacaine and hyperbaric tetracaine, there is as yet no consensus as to whether there are or are not ongoing differences between the 2 local anesthetics and, if so, in which direction.

Gielen et al. (16), in comparing glucose-free 0.5% and 0.75% bupivacaine with hyperbaric (8% glucose) 0.5% bupivacaine and 0.5% tetracaine, found no differences between the solutions with regard to mean maximum cephalad spread of analgesia to pinprick. Mean decreases in blood pressure were in the range of 10–20%, with decreases in heart rate of 5–10% in all groups. Also, the percent decrease in systolic blood pressure 10 min after injection was significantly greater with tetracaine and 0.75% bupivacaine than it was with hyperbaric 0.5% bupivacaine. Bigler et al. (17) compared 0.5% hyperbaric tetracaine and bupivacaine and found a significantly greater decrease in mean arterial pressure after tetracaine, but no significant difference in changes in heart rate. In their study, plasma catecholamine levels, measured as an index of the level of sympathetic blockade, increased during bupivacaine spinal, a change interpreted as indicative of a compensatory increase in adrenergic activity in response to hypotension, whereas the patients receiving tetracaine showed no change in plasma norepinephrine levels. In the same study, the onset and spread of sensory (pinprick) and temperature block were not significantly different with bupivacaine and tetracaine. Axelsson and Widman (18), in comparing glucose-free bupivacaine (22.5 mg) with hyperbaric bupivacaine (20 mg) or tetracaine (15 mg) found levels of analgesia (pinprick testing) higher in both bupivacaine groups than in the tetracaine groups. A decrease in blood pressure of >30% of the initial value was found in 5% of the patients in the bupivacaine groups, whereas no patients in the tetracaine group had this level of hypotension.

No studies previous to the present one have investigated differences in the width of the zones of differential blockade during onset, maintenance, and regression of spinal anesthesia with either tetracaine or bupivacaine. This study is also the first to document the constancy of the zones of differential blockade during onset, maintenance, and offset of spinal anesthesia with both hyperbaric bupivacaine and tetracaine. Despite a tendency toward a difference between tetracaine and bupivacaine in the width of zones of differential blockade over time (Figures 1 and 2), this was not statistically significant, except for light touch-to-pinprick and light touch-to-temperature zones at 30 min (Table 1). Thus, this study demonstrates that the zones of differential sensory blockade are not a function of the maximal craniad extent of sensory denervation (Figure 3).

Since there were no statistically significant differences between the two groups in the mean maximal (i.e., most rostral) level of sensory denervation, and

since there also were no significant differences in the extent of sympathetic denervation as a function of the local anesthetic used, it is not surprising that there were no statistically significant differences in heart rate and blood pressure related to the local anesthetic used.

In summary, this study shows that at equivalent doses, hyperbaric spinal bupivacaine and tetracaine are similar with respect to mean maximal rostral spread, that width of the zones of differential blockade to light touch, pinprick, and temperature modalities is constant during onset, maintenance, and regression of spinal anesthesia, and that the choice of local anesthetic does not influence hemodynamic parameters.

References

1. Greene NM. Area of differential block in spinal anesthesia with hyperbaric tetracaine. Anesthesiology 1958;19:45–50.

2. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:11.

3. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Strichartz GR, ed. Local anesthetics. Berlin: Springer-Verlag, 1987:189–93.

4. Sinclair DC, Hinshaw JR. Sensory changes in procaine nerve block. Brain 1950;73:224–43.

5. Sarnoff SJ, Arrowood JG. Differential spinal block: a preliminary report. Surgery 1946;20:150–9.

6. Arrowood JC, Sarnoff SJ. Differential spinal block: V. Use in the investigation of pain following amputation. Anesthesiology 1948;9:614–22.

7. Gasser HS, Erlanger J. Role of fiber size in the establishment of nerve block by pressure or cocaine. Am J Physiol 1929; 88:581–91.

8. Helrich M, Papper EM, Brodie BB, Fink M, Rovenstine EA. The fate of intrathecal procaine and spinal fluid level required for surgical anesthesia. J Pharmacol Exp Ther 1950;100:78–82.

9. Kitahara T, Kuri S, Yoshida J. Spread of drugs used for spinal anesthesia. Anesthesiology 1956;17:205–8.

10. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 1952;117:500–44.

11. Strichartz G. Molecular mechanisms of nerve block by local anesthetics. Anesthesiology 1976;45:421–41.

12. Courtney KR. Mechanism of frequency-dependent inhibition of sodium currents in frog myelinated nerve by the lidocaine derivative GEA968. J Pharmacol Exp Ther 1975;195:225–36.

13. Courtney KR, Kendig JJ, Cohen EN. Frequency-dependent conduction block: the role of nerve impulse pattern in local anesthetic potency. Anesthesiology 1978;48:111–7.

14. Rocco AG, Mallampati SR, Boon J, et al. Double blind evaluation of intrathecal bupivacaine and tetracaine. Regional Anesth 1984;9:183–7.

15. Rocco AG, Raymond SA, Murray E, et al. Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. Anesth Analg 1985;64:917–23.

16. Gielen MJM, DeGrood PMRM, Edstrom HH, Crul JF. Comparison of bupivacaine and tetracaine for spinal anesthesia. Regional Anesth 1984;9:62-7.

17. Bigler D, Hjortso NC, Edstrom H, et al. Comparative effects of intrathecal bupivacaine and tetracaine on analgesia, cardiovascular function and plasma catecholamines. Acta Anaesthesiol Scand 1986;30:199-203.

18. Axelsson K, Widman GB. A comparison of bupivacaine and tetracaine in spinal anaesthesia with special reference to motor block. Acta Anaesthesiol Scand 1985;29:79-86.

Urodynamic Studies after Intrathecal Fentanyl and Buprenorphine in the Dog

Benjamin Drenger, MD and Florella Magora, MD

DRENGER B, MAGORA F. Urodynamic studies after intrathecal fentanyl and buprenorphine in the dog. Anesth Analg 1989;69:348–53.

Cystometrograms (CMG) and urethral pressure profiles (UPP) were used in six anesthetized dogs to study the urodynamic effects of intrathecal (IT) injections of fentanyl and buprenorphine. The CMG and UPP were examined for each of the two drugs in all dogs (four experiments per animal). The measurements were performed before and 15, 30, 60, 90, and 120 min after IT injection of either 1.5 μg/kg fentanyl or 2 μg/kg buprenorphine. Fifteen minutes after IT injection of fentanyl, reduction in bladder tone was already noted, followed by decreases in mean peak vesical pressure of 48.3% ± 6.0 (SE) (P < 0.05) and mean peak urethral pressure of 38% ± 3.0 (P < 0.05) between 30 and 60 min after injection. These decreases, occurring in each experiment, gradually lessened at 90 and 120 min. The effects of IT buprenorphine, a partial opioid agonist, on bladder and urethral dynamics were inconsistent and nonsignificant in all studies. Disturbances of micturition observed clinically after spinal opioid administration may be related to the decrease in intravesical pressure and the resulting highly compliant bladder. Relaxation of the urethral musculature seen 15 min after IT fentanyl may prevent overdistension of the bladder and its associated complications.

Key Words: KIDNEY, URODYNAMICS—spinal opioids. ANALGESICS, FENTANYL, BUPRENORPHINE. ANESTHETIC TECHNIQUES, SPINAL—fentanyl, buprenorphine.

Endogenous opioid peptides, as well as parenterally or spinally administered exogenous opioids, have significant effects on the reflexes that control function of the lower urinary tract (1–7). Clinically, this is manifested by disturbances of micturition characterized by urinary retention, especially when opioids are administered by intrathecal (IT) injection (7–10). Urodynamic studies in humans (11) and in laboratory animals (12,13) have demonstrated that epidural and IT morphine relaxes the smooth muscle of the bladder with little or no effect on the internal or external urethral sphincter. Moreover, as Durant and Yaksh (13) have shown, inhibition of micturition in unanesthetized rats parallels the analgesic effect of IT morphine and that voiding is accompanied by an increase in intravesical pressure that overcomes urethral resistance. However, not all opioids behave in a similar manner with regard to their action on the detrusor or urethral musculature (8). For example, IT methadone, in equianalgesic doses as morphine, increases the tone of the bladder wall in anesthetized dogs (12). This phenomenon may account for the reduced incidence of urinary retention reported after epidural methadone analgesia in humans (14–17), as compared with morphine (9–11). The frequency of urinary disturbances associated with other IT narcotics, such as pentazocine (18), fentanyl (19,20), and buprenorphine (21–23) is also less than that seen after morphine. However, the effects of these drugs on the lower urinary tract have not previously been investigated.

In an attempt to elucidate the underlying reason for the low occurrence of urinary problems after spinal analgesia with fentanyl and buprenorphine, cystometrograms (CMG) and urethral pressure profiles (UPP) studies were used in dogs given IT injection of either of these drugs to determine effects on the detrusor muscle and on the urethra.

Materials and Methods

Twenty-four CMG and UPP urodynamic studies were carried out in six 13–20-kg anesthetized female

mongrel dogs, before and after IT injection of fentanyl and buprenorphine, in separate randomized experiments in the same dog.

These experiments do not involve painful surgical stimulation. Anesthesia induced by intravenous (IV) pentobarbital (25 mg/kg), and followed by tracheal intubation, was maintained by mechanical ventilation using nitrous oxide (N_2O) and oxygen. In order to exclude the effect of changing intraabdominal pressure on the urinary bladder, pancuronium bromide (0.1 mg/kg) was used to produce complete muscle paralysis. The latter was confirmed before each study by measuring responses to motor nerve stimulation with supplementary doses of pancuronium given as indicated. In contrast to pentobarbital, N_2O and pancuronium have only a negligible effect on the urinary tract, and thus do not influence urodynamic responses (24,25).

To assure that whatever effect pentobarbital might have on the bladder would be minimal and relatively constant, all urodynamic studies commenced 90 min after induction of anesthesia. Electrocardiogram and body temperature were monitored continuously and normoventilation was confirmed by arterial blood gas analysis. At the end of each experiment the dogs, although responding to stimuli and able to move, remained somnolent for at least an additional hour. An interval of 1 week was allowed between experiments in the same dogs to ensure complete recovery of the bladder from the previous mechanical or drug effects. Each dog underwent four separate experiments. Neither neurological deficit nor signs of infection were noted throughout the experimental period.

The urodynamic measurements were recorded immediately before and 15, 30, 60, 90, and 120 min after IT injection of either fentanyl (1.5 μg/kg) or buprenorphine (2 μg/kg) diluted in saline to 1-mL volumes. The IT injection was made through a fine needle at the L2-3 or L3-4 interspace; correct placement of the needle was confirmed by the appearance of cerebrospinal fluid (CSF).

The accuracy and reproducibility of this canine model was previously demonstrated using IT saline (12).

The CMG studies consisted of continuous filling of the bladder with saline and simultaneous measurement of the intravesical pressure using a double-lumen bladder catheter (French 10), introduced via the urethra. The catheter was perfused through one arm with normal saline at a constant rate of 40 mL/min by means of a Harvard syringe pump, while the other arm was connected to a pressure transducer and a two-channel recorder (model 7702B, Hewlett-Packard Co., Palo Alto, CA). During filling the pres-
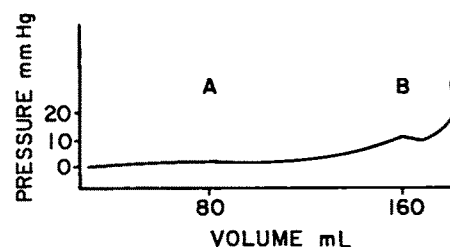
Figure 1. Representative cystometrogram before drug administration. A, point halfway to the maximal chosen volume; B, maximal chosen volume point; C, overfilling is imminent, and infusion is halted. In all experiments, drug effect was compared, before and after IT injection, at points A and B.

sure in the bladder increased gradually until a sharp incline in the plotted curve indicated that overfilling was imminent (Figure 1, point C), at which point infusion was halted before voiding occurred and before the stretched fibers of the detrusor muscle could be damaged (12,26). The pressure values at two points on the curve—at the maximal chosen volume (point B) and after instillation of half this volume (point A)—were compared before and after IT opioid injection to assess the effect of the drug. Detrusor compliance was then calculated by dividing the volume by the pressure measured at the two chosen points on the curve. The method of evaluating CMG changes has been described in detail previously (12).

Statistical analysis of the vesical pressure and compliance data was performed by the Wilcoxon matched-pairs test with unpredicted direction (two tails). In order to overcome the individual variation between dogs, primarily attributed to weight and diurnal differences, the same dog was tested with each of the drugs, in separate experiments. The change in pressure (in millimeters of mercury [mm Hg] and in percentages) after each drug administration was calculated, and the comparison between the fentanyl and buprenorphine effects was evaluated again for significance applying the Wilcoxon matched-pairs test with unpredicted direction.

For the UPP studies a specially designed catheter was used (27), with a sealed distal tip and two minute holes on either side to allow infusion of fluid and recording of pressures between the catheter and the walls of the urethra. The catheter was introduced into the empty bladder and then, with continuous perfusion of 2 mL/min, it was withdrawn at a constant speed of 1.5 cm/min, so that the pressure profile was recorded along the entire length of the urethra (Figure 2). The maximal closure pressures at the bladder neck were compared before and after drug administration at the above mentioned time intervals. Statistical analysis was performed using the Wilcoxon matched pairs test with unpredicted direction. The
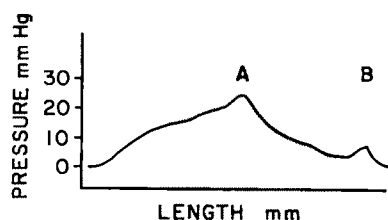
Figure 2. Representative urethral pressure profile. A, maximal pressure at the bladder neck (the pressure at this point was used as reference for the comparison of urethral pressure profile measurements); B, pressure at external sphincter depressed by the effect of the muscle relaxant.
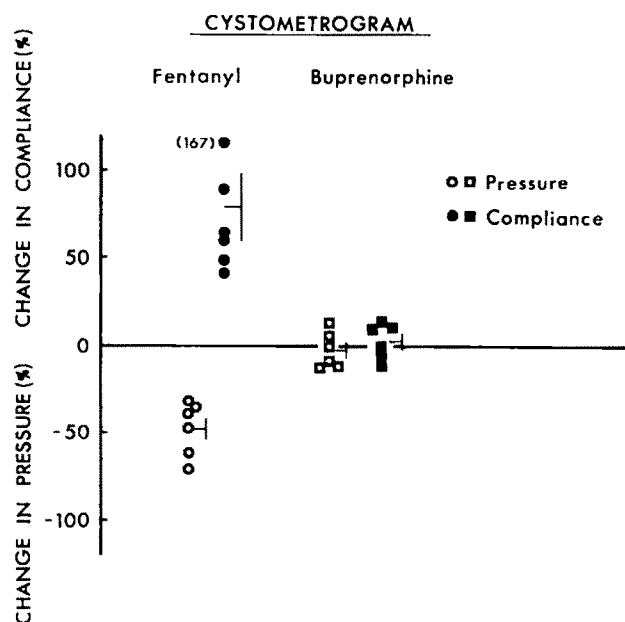
Figure 3. Percent change in pressure and compliance at maximal chosen volume, in the 60-min cystometric studies after IT administration of fentanyl and buprenorphine in the same six dogs.

effects of both drugs was compared by means of the same test.

Results

Cystometrogram

In all studies, clear evidence of a marked depression of the CMG pressure curve for the two selected volumes was observed after IT fentanyl administration, whereas IT buprenorphine had only a negligible effect on the intravesical pressure in each experiment (Figure 3). The measurements of the maximal chosen volume varied widely between dogs of different weights, ranging between 150 and 300 mL.

The appearance of bladder relaxation after IT fentanyl injection was already evident at the 15-min measurement, becoming maximal at 60 min, with a

mean of 48.3% ± 6% (SE) reduction in pressure from 18.5 ± 5 to 10.1 ± 5 mm Hg ($P < 0.05$) (Table 1). A similar increase in detrusor compliance of 79% ± 19% ($P < 0.05$) was calculated. The 90- and 120-min measurements showed a gradual lessening of the effects of the drugs though it was still evident at the termination of the experiment. The difference between the two drugs in their effects on intravesical pressure represented a significant difference ($P < 0.05$) in their actions on the bladder detrusor muscle.

After administration of IT fentanyl, the trend of depression in the CMG pressure curve at the half-volume measurement resembled that observed at maximal chosen volume in all instances. The maximal reduction of the mean intravesical pressure at 60 min was 32% ± 10% ($P = 0.06$), at which time the effect of fentanyl on the detrusor was significantly more pronounced than was that of buprenorphine ($P < 0.05$).

Urethral Pressure Profile

Similar to its effect on the bladder wall, IT fentanyl resulted in significant relaxation of the urethral musculature in each dog ($P < 0.05$), an effect observed within 15 min of injection, that became maximal at 30 min when it had decreased from a mean baseline value of 36.3 ± 3 to 22.6 ± 2.7 mm Hg (a reduction of 38% ± 3%). There was no statistically significant effect of IT buprenorphine on the urethral tone (Figure 4). The mean maximal closure pressure was 32 ± 3 mm Hg before and 36 ± 4 mm Hg after IT buprenorphine. The effect of buprenorphine on urethral tone was also not consistent in different dogs: in three dogs there were a small decrease in the UPP, whereas in the other three animals these were slight increases. This inconsistency was also noted during the course of single experiments.

Discussion

The results of the present investigation demonstrate that in dogs IT fentanyl affects the muscular activity of the smooth muscle of both bladder and urethral junction. Soon after the IT injection of fentanyl, and continuing for at least 2 hr, the detrusor muscle relaxed, leading to the development of highly compliant vesical walls and, so, to accommodation of larger volumes of fluid in the bladder at any given pressure. The influence of IT fentanyl on the canine detrusor is thus similar to the changes in vesical tonus reported after IT or epidural morphine in humans (11), dogs (12,28), and rats (5,13,29), but

Table 1. Cystometric Pressures and Calculated Compliances after Intrathecal Fentanyl and Buprenorphine in Six Dogs

	Drug	Before Injection	After Injection (min)			P value
			30	60	90	
Pressure at maximal	F	18.5 ± 5	12.3 ± 5	10.1 ± 5	12.3 ± 4	<0.05
volume (mm Hg)	B	14.3 ± 2	14.3 ± 2	14.5 ± 3	14.3 ± 2.5	NS
Pressure at half	F	8.8 ± 0.8	7.6 ± 1.3	6 ± 1	7.9 ± 1	<0.06[a]
volume (mm Hg)	B	6.9 ± 0.8	7.2 ± 0.7	7.5 ± 0.7	8.5 ± 1	NS
Compliance at maximal	F	7.6 ± 2	14.9 ± 7	18.3 ± 6	13.7 ± 6	<0.05
volume (mL/mm Hg)	B	10.1 ± 3	10 ± 3	11.1 ± 4	10.1 ± 3	NS

Values presented as mean ± SEM. P value—for comparing values at each time interval vs baseline. Abbreviations: B, buprenorphine; F, fentanyl; NS, nonsignificance.
[a] At 60 min only.

URETHRAL PRESSURE PROFILE
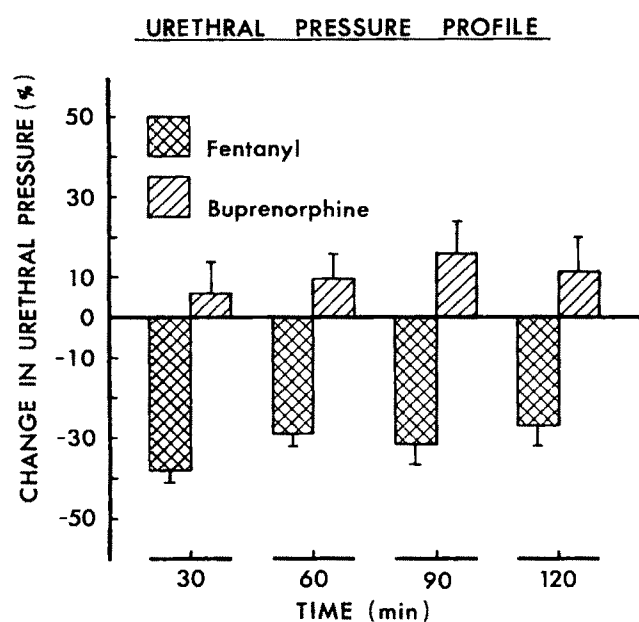
Figure 4. Mean percent change (±SE) in urethral pressure profile studies performed at 30-, 60-, 90-, and 120-min intervals after IT administration of fentanyl and buprenorphine in the same six dogs.

differs from the action of IT methadone in dogs (12), IT naloxone in rats (5), and IV naloxone and IV physostigmine in the same animal model as used in the present study (30) (Table 2). Bladder hypotonicity leading to inhibition of the volume-evoked micturition reflex has been implicated in bladder dysfunction, as manifested in the urinary disturbances commonly seen after spinal morphine analgesia (11,13). The administration of the opioid antagonist naloxone promptly reverses this complication by restoring effective vesical contractions (9).

In addition to its effects on the bladder wall proper, IT fentanyl caused pronounced relaxation of the bladder neck musculature (also known as the internal urethral sphincter). Possibly, the decrease in urethral resistance may partially counteract the effect

of IT fentanyl on micturition, an effect that might explain the observation that the incidence of urinary retention in human subjects is less after spinal analgesia with IT fentanyl than it is with other opioids (19,20). The overall effect of IT fentanyl on spontaneous voiding is difficult to ascertain from the present experiments in anesthetized dogs. However, Durant and Yaksh (13) found, using an awake rat model, with chronically implanted bladder cannulae, that after IT morphine dribbling of fluid from the bladder occurred only when the intravesical pressure exceeded the resistance of the urethral pressure.

Another important factor relates to the fact that fentanyl is shorter in duration of action and is more highly lipid soluble than morphine. This accounts for the more rapid onset of action of fentanyl and its more rapid clearance, as well as for the low free-drug concentration in the CSF (9), and, thus, reduced migration to the supraspinal centers in the brain that mediate urinary tract control.

The effect of intrathecal opioids on the lower urinary tract function has been related to various modes and sites of action. One suggestion is that opioids block receptor groups that modulate the neurogenic control of the bladder function at the spinal level. This decrease in spinal receptor activity depresses the preganglionic neurons of the sacral parasympathetic pathways with ensuing diminution of cholinergic discharge by efferent parasympathetic pelvic nerves that innervate bladder muscles (13). The relaxation of the urethral musculature, which is effected mainly by way of the sympathetic nervous system, may be attributed to the potent sympatholytic property of fentanyl (31). This possibility is strengthened by the demonstration that another sympathetic reflex—the gastrointestinal—is inhibited by epidural fentanyl administration (32).

Another possible mode of action of spinal opioids on the lower urinary tract is that, through their antinociceptive activity, they impair transmission in

Table 2. Urodynamic Effect after Systemic and Spinal Administration of Opioids

Opioid	Administration	Model	Detrusor Tone	Urethral	Reference No.
Agonist					
Morphine	Epidural	Human	Decreased	No effect	11
	IT	Dog	Decreased	No effect	12, 28
Methadone	IT	Dog	Increased	No effect	12
Fentanyl	IT	Dog	Decreased	Decreased	a
Partial agonist					
Buprenorphine	IT	Dog	No effect	No effect	a
Antagonist					
Naloxone	IT	Rat	Increased	Not measured	5
Naloxone	IV	Human	Increased	Decreased	1
Physostigmine	IV	Dog	Increased	Not measured	30

aPresent study.

the sensory primary afferent component of this region (1,5,8).

Compared with IT fentanyl, IT buprenorphine had no significant effect on either the bladder tone or the urethral closure, as expressed by the CMG and UPP pressure curves. The difference in action of this partial agonist may be ascribed to the dose that was employed. In the case of an agonist–antagonist drug, the dosage administered is of particular importance in determining side effects. It is possible that in the present study the dosages of IT fentanyl and IT buprenorphine were not equianalgesic. However, the selection of the buprenorphine dose was based on clinical investigations that compared its analgesic potency with that of morphine (21,22,33). In a controlled study of continuous as well as on-demand epidural infusion of buprenorphine in humans, its analgesic potency ratio as compared with morphine was found to be 8 (31), whereas in other comparable studies fentanyl had a potency ratio of 10-1, again in comparison with morphine (34,35). It should be noted that similar doses of IT morphine produce similar effects in the urinary tracts of humans and dogs (8,12). All these data guided us in selecting the dosages of the two drugs used in the present study. Admittedly, allowance must be made for errors when extrapolating the present findings regarding the effects of different drugs on the urinary systems of different species. The use of more than one dose regimen may help clarify our findings.

Another explanation for the difference in effects on bladder and urethral musculature compliance after either IT fentanyl or IT buprenorphine that we observed may be due to the heterogeneity of receptor populations influenced by each agent. Dray and Metsch (5) in studies of the specific influence of drugs with selective receptor affinity on the bladder wall found that μ- and δ-receptor agonist drugs caused bladder relaxation, whereas the κ-receptor agonists

did not affect the vesical muscles. The results of the present investigation are in agreement with these observations. Fentanyl, like morphine, which has a high μ activity, caused marked urinary tract inhibition, in contrast to buprenorphine; the lack of any effect of this drug on urinary dynamics may reflect the fact that it is a partial agonist with relatively nonselective affinity for μ-, δ-, and κ-receptors in the spinal cord (36).

The relaxation of bladder and urethral musculature associated with the IT administration of fentanyl and the lack of effects by IT buprenorphine on these structures may explain the reduced urinary complications observed in people after spinal analgesia with these drugs. Their use may be particularly warranted, therefore, in patients in whom urinary disturbances might constitute a complication to be particularly avoided.

References

1. Murray KHA, Feneley RCL. Endorphins—a role in lower urinary tract function? The effect of opioid blockade on the detrusor and urethral sphincter mechanism. Br J Urol 1982; 54:638–40.

2. Simonds WF, Booth AM, Thor KB, Ostrowski NL, Nagel JR, de Groat WC. Parasympathetic ganglia: naloxone antagonizes inhibition by leucine-enkephalin and GABA. Brain Res 1983; 271:365–70.

3. Thor KB, Roppolo JR, de Groat WC. Naloxone induced micturition in unanesthetized paraplegic cats. J Urol 1983;129:202–5.

4. Hisamitsu T, de Groat WC. The inhibitory effect of opioid peptides and morphine applied intrathecally and intracerebroventricularly on the micturition reflex in the cat. Brain Res 1984;298:51–65.

5. Dray A, Metsch R. Inhibition of urinary bladder contractions by a spinal action of morphine and other opioids. J Pharmacol Exp Ther 1984;231:254–60.

6. Yaksh TL, Noueihed R. The physiology and pharmacology of spinal opiates. Annu Rev Pharmacol Toxicol 1985;25:433–62.

7. Yaksh TL. Spinal opiates analgesia: characteristics and principles of action. Pain 1981;11:293–346.

8. Dray A. Epidural opiates and urinary retention: new models provide new insights. Anesthesiology 1988;68:323–4.

9. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.

10. Petersen TK, Husted SE, Rybro L, Schurizek BA, Wernberg M. Urinary retention during I.M. and extradural morphine analgesia. Br J Anaesth 1982;54:1175–8.

11. Rawal N, Mollefors K, Axelsson K, Lingardh G, Widman B. An experimental study of urodynamic effects of epidural morphine and naloxone reversal. Anesth Analg 1983;62:641–7.

12. Drenger B, Magora F, Evron S, Caine M. The action of intrathecal morphine and methadone on the lower urinary tract in the dog. J Urol 1986;135:852–5.

13. Durant PAC, Yaksh TL. Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats. Anesthesiology 1988;68:325–34.

14. Welch DB, Hrynaszkiewicz A. Postoperative analgesia using epidural methadone: administration by the lumbar route for thoracic pain relief. Anaesthesia 1981;36:1051–4.

15. Beeby D, MacIntosh KC, Bailey M, Welch DB. Postoperative analgesia for Caesarean section using epidural methadone. Anaesthesia 1984;39:61–3.

16. Evron S, Samueloff A, Simon A, Drenger B, Magora F. Urinary function during epidural analgesia with methadone and morphine in postcaesarean section patients. Pain 1985;23:135–44.

17. Magora F, Cotev S. Future trends in regional spinal opioids. Int Anesthesiol Clin 1986;24:113–20.

18. Kalia PV, Madan R, Saskena R, Batra RK, Gode GR. Epidural pentazocine for postoperative pain relief. Anesth Analg 1983;62:949–50.

19. Welchew EA, Thronton JA. Continuous thoracic epidural fentanyl: a comparison of epidural fentanyl with intramuscular papaveratum for postoperative pain. Anaesthesia 1982;37:309–16.

20. Rucci FS, Cardamone M, Migliori P. Fentanyl and bupivacaine mixtures for extradural blockade. Br J Anaesth 1985;57:275–84.

21. Lanz E, Simko G, Theiss D, Glocke MH. Epidural buprenorphine—a double-blind study of postoperative analgesia and side effects. Anesth Analg 1984;63:593–8.

22. Bilsback P, Rolly G, Tampubolon O. Efficacy of the extradural administration of lofentanil, buprenorphine or saline in the management of postoperative pain: a double-blind study. Br J Anaesth 1985;57:943–8.

23. Gundersen RY, Andersen R, Narverud G. Postoperative pain relief with high-dose epidural buprenorphine: a double-blind study. Acta Anaesthesiol Scand 1986;30:664–7.

24. Doyle PT, Briscoe CE. The effects of drugs and anaesthetic agents on the urinary bladder and sphincters. Br J Urol 1976;48:329–35.

25. Yaksh TL, Durant PAC, Brent CR. Micturition in rats: a chronic model for study of bladder function and effect of anesthetics. Am J Physiol 1986;251:R1177–85.

26. Hinman F. Postoperative overdistention of the bladder. Surg Gynecol Obstet 1976;142:901–2.

27. Brown M, Wickham JEA. The urethral pressure profile. Br J Urol 1969;41:211–7.

28. Magora F, Shazar N, Drenger B. Urodynamic studies after intrathecal administration of baclofen and morphine in dogs. J Urol 1989;141:143–7.

29. Durant PAC, Yaksh TL. Epidural injections of bupivacaine, morphine, fentanyl, lofentanil, and DADL in chronically implanted rats: a pharmacologic and pathologic study. Anesthesiology 1986;64:43–53.

30. Drenger B, Caine M, Sosnovsky M, Magora F. Physostigmine and naloxone reverse the effect of intrathecal morphine on the canine urinary bladder. Eur J Anaesth 1987;4:375–82.

31. Bailey PL, Stanley TH. Pharmacology of intravenous narcotic anesthetics. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1986:745–97.

32. Lisander B, Stenqvist O. Epidural fentanyl counteracts sympathetic gastric inhibition. Acta Anaesthesiol Scand 1985;29:560–5.

33. Chrubasik J, Vogel W, Trötschler H, Farthmann EH. Continuous-plus-on-demand epidural infusion of buprenorphine versus morphine in postoperative treatment of pain. Drug Res 1987;37:361–3.

34. Chrubasik J, Wüst H, Schulte-Mönting J, Thon K, Linbler M. Relative analgesic potency of epidural fentanyl, alfentanil and morphine in treatment of postoperative pain. Anesthesiology 1988;68:929–33.

35. Kay B. Postoperative pain relief. Anaesthesia 1981;36:949–51.

36. Villger JW. Binding of buprenorphine to opiate receptors. Regulation of guanyl nucleotides and metal ions. Neuropharmacology 1984;23:373–5.

Nitrogen-Sparing Effect of Epidural Administration of Local Anesthetics in Colon Surgery

Catherine Vedrinne, MD, Jean M. Vedrinne, MD, Michel Guiraud, MD, Marie C. Patricot, MD, and Paul Bouletreau, MD

VEDRINNE C, VEDRINNE JM, GUIRAUD M, PATRICOT MC, BOULETREAU P. Nitrogen sparing effect of epidural administration of local anesthetics in colon surgery. Anesth Analg 1989;69:354–9

A nitrogen-sparing effect of epidural anesthesia has been clearly demonstrated in gynecological and lower abdominal surgery. To determine if epidural anesthesia also has a protein-sparing effect during major upper or mid-abdominal surgery, postoperative nitrogen balance and 3-methylhistidine urinary excretion (an index of skeletal muscle protein catabolism) were measured for 6 days in 28 patients who had undergone colon resection for cancer with general anesthesia (N_2O-O_2-1% enflurane) either supplemented with low dose fentanyl plus intermittent systemic pentazocine for postoperative pain (n = 13), or the same general anesthetic plus epidural injection of either etidocaine 1% intraoperatively and bupivacaine 0.25% postoperatively (n = 8) or meperidine (n = 7) for 48 hr after skin incision. The cumulative 6-day nitrogen balance and the cumulative 3-methylhistidine urinary excretion were significantly less after epidural injection of etidocaine intraoperatively and bupivacaine postoperatively than in the two other groups. There was a significant correlation between the daily urinary excretion of 3-methylhistidine and the daily nitrogen balance in the three groups. This study suggests that in colon surgery, epidural analgesia with local anesthetics in the postoperative period improves nitrogen balance and this effect takes place partly in the muscle.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. METABOLISM, NUTRITION— postoperative.

Surgical stress induces endocrine metabolic responses (1,2) including protein catabolism leading to negative nitrogen balance and potential delayed healing of surgical wounds. Local anesthetics providing operative epidural blockade can, it is generally agreed, prevent a major part of the endocrine and metabolic changes following lower abdominal and gynecologic operations as well as surgery on the lower extremities if the level of anesthesia extends from T4 to S5 and if the epidural anesthesia is initiated before the skin incision is made (3–5). Glucose tolerance is improved (6,7), postoperative nitrogen balance is better maintained (8), and the normal increase in postoperative oxygen consumption is lessened (9). The effects of epidural anesthesia on metabolic responses to major intra-abdominal (especially upper-abdominal) surgery are not as clear, however (10–13).

Since data on the nitrogen-sparing effect of epidural anesthesia are scanty, we studied nitrogen balance and 3-methylhistidine urinary excretion (as a marker of skeletal muscle protein catabolism) in three groups of patients undergoing colon resection: those having general anesthesia followed by parenteral narcotics for relief of postoperative pain and those having general anesthesia supplemented intraoperatively and followed postoperatively by epidural injection of either narcotics or local anesthetics for relief of postoperative pain.

Patients and Methods

Thirty-two patients scheduled for colon surgery (but not abdominoperineal resection) for cancer were included in the study. None had cardiac, hepatic, or renal disease. The study protocol was approved by our ethical committee, and informed consent was obtained preoperatively from all patients. Four pa-

tients were excluded because of surgical or infectious complications, or temperature over 38.5°C during the 6-day study. Of the remaining 28 patients (mean age 67.4 ± 13 years), 13 were prospectively assigned to a group to be given systemic narcotics for relief of postoperative pain (Group I). The remaining patients were given epidural meperidine (Group II; $n = 8$) or epidural local anesthetics (Group III; $n = 7$) for relief of postoperative pain.

An epidural catheter was inserted between the second and the third lumbar vertebrae on the day before surgery in all patients in Groups II and III. X-rays following injection of a small amount of contrast material through the epidural catheter and response to injection of a small test dose of 2% lidocaine with epinephrine before induction of anesthesia were used to confirm the position of the catheter. All operations started between 7:30 and 8:30 AM. All patients were premedicated with intramuscular atropine (0.5 mg) and diazepam (10 mg). General anesthesia was induced in all patients with intravenous thiopental (5–7 mg/kg), and then maintained using 50% nitrous oxide in oxygen and 1% enflurane; tracheal intubation was facilitated by pancuronium (0.1 mg/kg). In Group I, however, general anesthesia was supplemented with a low dose of fentanyl (3 µg/kg) with subsequent 1.5 µg/kg doses every 30 min throughout the operation. In Group II, general anesthesia was supplemented with the epidural injection of meperidine (2 mg/kg) 30 min before skin incision with subsequent injection of 1 mg/kg every 30 to 40 min throughout the operation. In Group III, general anesthesia was supplemented with the epidural injection of 1% etidocaine 30 min before skin incision to provide sensory analgesia from T4 to S5. The volume of 1% etidocaine injected was the minimum number of milliliters required to reach the fourth thoracic segment calculated as described by Bromage (14). Half the initial dose was thereafter injected every 30 to 40 min throughout the operation.

Postoperative analgesia was maintained for 48 hr, beginning after closure of the skin incision by administration of analgesics every 4 hr for the first 24 hr and then on demand but never with less than 4 hr between administrations. In Group I the analgesic consisted of IM pentazocine injection (0.5 mg/kg). In Group II it consisted of epidural injection of meperidine (0.5 mg/kg). In Group III it consisted of epidural injection of bupivacaine 0.25% in volumes equieffective to the amount of etidocaine used to maintain intraoperative analgesia.

All patients came to the operating room in a postabsorptive state after fasting for 24 hr, and after preoperative colic preparation. Water and electrolyte

equilibrium was restored using intravenous infusions of 5% glucose in water, isotonic saline and albumin, if necessary. Sympathomimetics and insulin were avoided. All patients had total parenteral nutrition for day 0 through day 5 consisting of 30 kcal (50% carbohydrates and 50% fat) and 0.18 g nitrogen (L-amino acid solution containing 48% essential amino acids and 22% of branched chain amino acid; Vintene ® Cernep Synthelabo) per kg per day.

The nutritional status of each patient was assessed by recording weight, weight/height index, and serum levels of both albumin and short half-life proteins (serum prealbumin, serum retinol binding protein [RBP], and serum C3 complement). The bladder was catheterized in all patients and 24-hr urine collections made. Each day, 100 mL urine sample was obtained and immediately frozen (−25°) and stored. Within 2 months all samples were assayed. Nitrogen loss was calculated daily as the sum of the urinary nitrogen (measured using the Kjeldhal method), the nonurinary nitrogen loss (estimated at 2g/day) and the change in body urea nitrogen during the 24-hr period. The change in body urea nitrogen was calculated as follows: total body water at the onset of collection (L) × change in serum urea nitrogen (g/L). Total body water in liters was estimated to be 60% of the body weight. Daily urinary excretion of 3-methylhistidine (3-MH) was measured by gas phase chromatography (15) from day 0 to day 5.

Data are presented as mean values plus or minus standard error of mean (SEM). Statistical analysis was performed using the Mann–Whitney test. The method of least squares was used for estimating the coefficients in the regression equation and the variance analysis. Probability values <0.05 were considered to be statistically significant.

Results

The three groups were comparable as regards age, sex, weight, duration of surgery, and preoperative nutritional status (Table 1).

Postoperative pain relief required 115 ± 18 mg of pentazocine in Group I, 299 ± 44 mg of meperidine in Group II, and 184 ± 32 mg of bupivacaine in Group III.

In Group III the nitrogen balance was positive on day 0, and day 1, and near zero on days 4 and 5 (Table 2). Nitrogen loss was greatest on days 2 and 3 in Group III, and on days 3, 4, and 5 in groups I and II. The differences between Group III and the two other groups were statistically significant on the fourth postoperative day and between groups II and III on the fifth postoperative day.

Table 1. Characteristics of the Patients

	Group I	Group II	Group III
n	13	8	7
Sex: male/female	9/4	5/3	4/3
Age (years)	66 ± 4	65 ± 4	73 ± 4
Body height (cm)	168 ± 3	172 ± 3	168 ± 3
Body weight (kg)	65.4 ± 3.6	67.5 ± 4.5	63 ± 5
Duration of surgery (min)	176 ± 8	162 ± 11	165 ± 16
Complement C3 (gr/L)	1.04 ± 0.06	1.12 ± 0.07	1.05 ± 0.04
RBP (gr/L)	0.047 ± 0.003	0.042 ± 0.004	0.053 ± 0.009
Serum prealbumin (gr/L)	0.26 ± 0.02	0.26 ± 0.03	0.27 ± 0.03
Serum albumin (gr/L)	43.2 ± 2.3	41.8 ± 3.4	53 ± 9

Group I: general anesthesia; Group II: epidural meperidine group; Group III: epidural local anesthetics. (X ± sem)

Cumulative nitrogen balance for 6 days (Figure 1) was negative in groups I (−13.9 ± 4.5 gr) and II (−17.7 ± 4 gr) but balanced in Group III (−0.2 ± 3 gr). Cumulative nitrogen balance was significantly different between groups II and III on day 1. On days 4 and 5 the differences between groups I and III and between groups II and III were statistically significant. There was no statistically significant difference in nitrogen excretion in groups I and II.

Daily urinary excretion of 3-MH in groups II and III was significantly different from day 0 to day 5 (Table 3). Differences between groups I and III were significant only on day 0, day 4, and day 5.

Differences in cumulative 3-MH urinary excretion (Figure 2) were statistically significant between groups II and III from day 0 to day 5 and between groups I and III on days 4 and 5. There was no statistically significant difference in cumulative 3-MH excretion in groups I and II.

There was a statistically significant negative correlation between nitrogen balance and 3-MH urinary excretion among the three groups (Group I: $r = -0.41$; Group II: $r = -0.37$; Group III: $r = -0.64$) (Figure 3).

Serum levels of retinol binding protein, prealbumin, and C3 complement decreased in all groups throughout the study without, however, significant differences among the three groups or within the same group between pre- and postoperative values.

Discussion

Although all patients had cancer, none suffered from malnutrition (including protein-calorie malnutrition), as shown by the normal range of anthropometric indices (weight, weight/height), and normal levels of serum albumin, RBP, C3, and prealbumin. The latter proteins have been termed "acute phase proteins" or more recently as "negative acute phase reactants" (16) based on the pattern of the decrease in their plasma levels following tissue damage. In our three groups of patients, these acute phase proteins were still at a low level by the fifth postoperative day due to the postoperative stress response, regardless of the type of pre- and postoperative analgesia used. Total parenteral nutrition was ineffective in restoring protein levels in all groups.

Nitrogen balance reflects the efficacy of parenteral nutrition, even if one does not know the type or source of nitrogen used. Our study shows that postoperative nitrogen balance could be improved in Group III. The 6-day cumulated nitrogen balance was nearly zero in Group III as of day 4. Because intake and nutritional status were the same in the three groups, the nitrogen-sparing effect was the result of epidural analgesia with local anesthetics. Moller et al. (3) and Kehlet et al. (4) point out that if epidural analgesia with local anesthetics is to inhibit endocrine and metabolic responses to gynecological surgery, it must be initiated at least 30 min before the start of surgical procedure and extend from dermatomes T4 to S5. This was done in our study: the correct position of the catheter was assessed by radiography, and the first dose injected 30 min before skin incision in large enough quantities to reach T4. The epidural narcotic (meperidine), even when reinforced intraoperatively with enflurane, was, however, unable to block metabolic responses to surgery as evidenced by the fact that the cumulative nitrogen balance was worst in Group II. Yet, in our study, we do not know if postoperative pain relief was equal in the three groups because we did not use a pain scale. However, Jorgensen et al. (17) showed that even though epidural morphine is better than conventional parenteral narcotics for relief of postoperative pain, blockade of somatic sensory pathways alone is inadequate in terms of mitigation of the metabolic response to pain. Thus, postoperative changes in blood hormone levels are poorly blocked by epidural narcotics (17,18). The effect of epidural analgesia with local anesthetics on the postoperative nitrogen loss that we observed in this study of patients undergoing colon surgery is probably due to the ability of local anesthetics to inhibit the release of catabolic hormones (catecholamines, cortisol, glucagon) as shown by Tsuji et al. (13) in patients having elective gastrectomies.

In our study the epidural catheter was removed 48 hr after surgery. The nitrogen-sparing effect per-

Table 2. Urinary Nitrogen Balance (g/day)

Group	Operative Day D0	Postoperative Days					Cumulative Nitrogen Balance
		D1	D2	D3	D4	D5	
I	−1.5 ± 1.3	−0.6 ± 1.3	−1.7 ± 0.7	−3.2 ± 0.8	−4.6 ± 1.3	−2.5 ± 1.1	−13.9 ± 4.5
II	−1.0 ± 1.7	−1.0 ± 1.0	−1.4 ± 0.5	−4.0 ± 1.9	−3.7 ± 1.3	−5.5 ± 1.4	−17.7 ± 4.0
II vs I	NS	NS	NS	NS	NS	NS	NS
III	+1.9 ± 0.5	+1.9 ± 1.0	−1.7 ± 1.5	−2.0 ± 1.4	+0.2 ± 1.3	−0.2 ± 1.3	−0.2 ± 3.0
III vs I	NS	NS	NS	NS	0.05	NS	0.05
III vs II	NS	NS	NS	NS	0.05	0.05	0.05

Group I: general anesthesia; Group II: epidural meperidine; Group III: epidural local anesthetics. (X ± SEM)
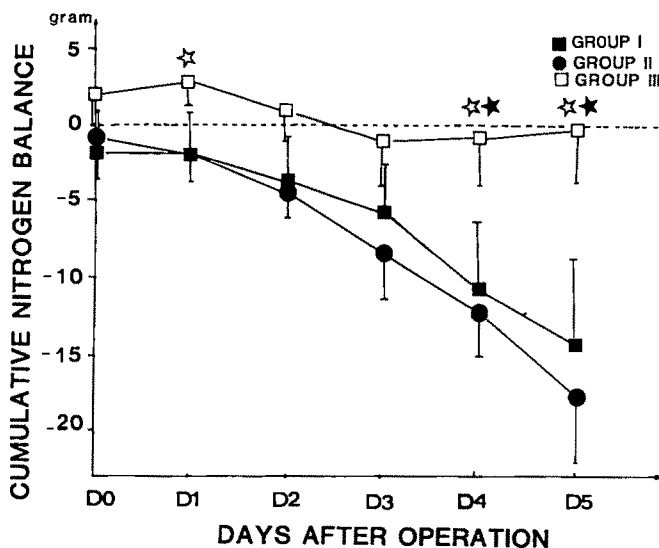
Figure 1. Cumulative nitrogen balance in patients undergoing colon surgery under general anesthesia supplemented by parenteral analgesia or epidural analgesia. Group I: parenteral analgesia; Group II: epidural meperidine; Group III: epidural local anesthetics. Values are mean ± SEM. ★ Group III vs Group I $P \leq 0.05$. ☆ Group III vs Group II $P \leq 0.05$.

sisted, however, into the fourth and the fifth postoperative days. This corroborates previous reports (8,12,13) of a long-lasting effect of the epidural analgesia. However, it seems that epidural analgesia has to be maintained for at least 24 hr postoperatively to achieve long-lasting effects (12).

The nitrogen-sparing effect of epidural analgesia with local anesthetics requires an adequate nutritional support. Thus, in gynecological surgery, Brandt and associates (8) found nitrogen balance on the first postoperative day to be negative when their patients received only isotonic saline solution intravenously. Hjortso et al. (11) concluded that epidural analgesia failed to prevent the nitrogen loss, but perhaps this was because caloric intake was low. Other discrepancies between our results and those of others may be due to others' inclusion both of different types of operations (in terms of duration and site of surgery) and of patients with and without

cancer, and their working with groups with different sex ratios.

Net nitrogen balance is easy to measure. More difficult is measurement of the proportions of muscular, plasma, and visceral proteins. Discovered in urine in 1955 by Tallen and Stein (19), 3-MH was identified as a constituent of both actin and myosin in muscle protein. Released after muscle protein breakdown, 3-MH is neither reutilized for protein synthesis nor metabolized. Free 3-MH is rapidly and entirely excreted in the urine (20). Part of 3-MH comes, however, from nonskeletal muscle tissue (gastrointestinal tract, heart, skin plus connective tissues, liver, brain, etc.) (21), but how much remains uncertain (22–24). Nonskeletal muscle 3-MH remains at low levels, however, especially in men and with diseases in which the rate of urinary excretion of 3-MH from muscle tissue increases. During intra- and postoperative stress, plasma level of 3-MH remains a reliable index of skeletal muscle catabolism. Gross et al. (25) have shown that elective surgical operations performed under general anesthesia are associated with statistically significant increases of up to 40% in the urinary excretion of 3-MH on the second and third postoperative days. In our study, the 3-MH urinary excretion increased in the second and third postoperative days, but the increase was significantly less in Group III. Moreover, 3-MH urinary excretion in Group III collected between day 0 and day 1 was significantly different than that in groups I and II. Despite a meat-free diet for only 24 hr before the measurement of 3-MH excretion, it seems that epidural analgesia with local anesthetics significantly reduces daily 3-MH urinary excretion in postoperative period. Epidural analgesia with narcotics (meperidine in the present instance) seems to be inadequate, probably because afferent nociceptive stimuli may override the analgesic effect of narcotic and because afferent stimuli may be transmitted through other neurogenic pathways (26). The cumulated urinary 3-MH excretion was significantly less in

Table 3. Urinary 3-Methylhistidine Excretion (μmol/day)

Group	Operative Day D0	Postoperative Days					Cumulative 3-Methylhistidine Excretion
		D1	D2	D3	D4	D5	
I	303 ± 55	319 ± 52	327 ± 43	373 ± 48	375 ± 49	306 ± 51	2005 ± 248
II	406 ± 66	389 ± 49	489 ± 58	450 ± 67	399 ± 62	442 ± 74	2575 ± 334
II vs I	NS	NS	NS	NS	NS	NS	NS
III	180 ± 20	207 ± 28	249 ± 35	215 ± 40	167 ± 43	163 ± 44	1203 ± 157
III vs I	0.05	NS	NS	NS	0.01	0.05	0.05
III vs II	0.05	0.05	0.01	0.05	0.05	0.01	0.05

Group I: General anesthesia; Group II: epidural meperidine; Group III: epidural local anesthetics. (X ± SEM)
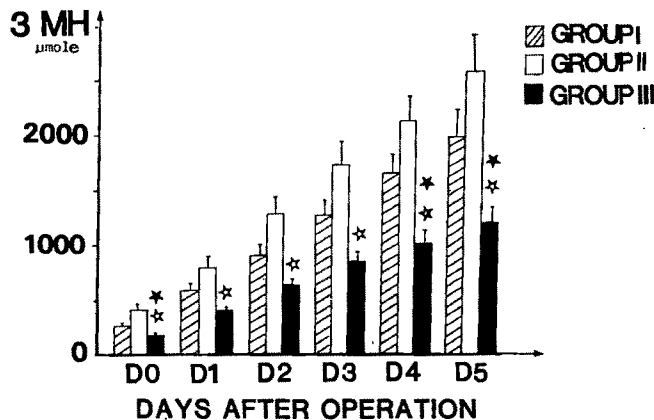
Figure 2. Cumulative 3-methylhistidine urinary excretion in patients undergoing colon surgery under general anesthesia, supplemented with parenteral analgesia or epidural analgesia. Group I: parenteral analgesia; Group II: epidural meperidine; Group III: epidural local anesthetics. Values are mean ± SEM. ★ Group I vs Group III $P \le 0.05$. ☆ Group II vs Group III $P \le 0.05$.
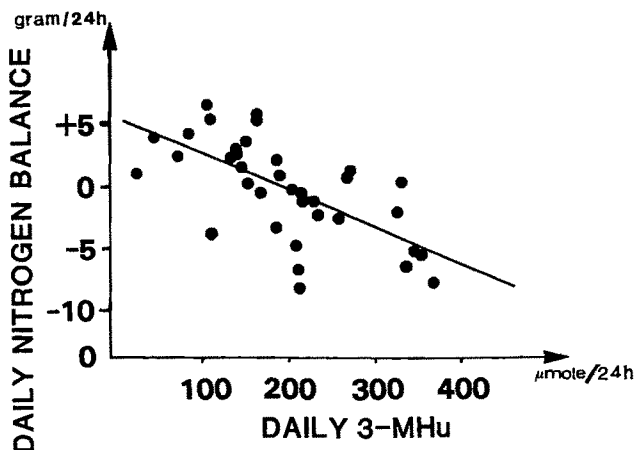
Figure 3. Correlation between daily 3-methylhistidine urinary excretion and daily nitrogen balance in local anesthetics group. ($r = -0.64$, $P \le 0.01$).

Group III by the fourth day, remaining low on the fifth, i.e., evidence of a muscular sparing effect. Moreover, there was a negative correlation between urinary excretion of 3-MH and nitrogen balance in the three groups, even though correlation is weak in

groups I and II. The correlation between urinary excretion of 3-MH and nitrogen balance was not observed by François et al. (27) but was confirmed in the study by Neuhäuser et al. (23). The nitrogen-sparing effect of epidural analgesia with local anesthetics seems to decrease catabolism of skeletal muscle proteins.

In conclusion, epidural analgesia with local anesthetics during and after colon surgery significantly improves the nitrogen balance of cancer patients without protein-calorie malnutrition. The muscles benefit from this sparing effect.

References

1. D'Athis F, Du Cailar J. Les conséquences neuroendocrinniennes et métaboliques du stress. Encycl méd. chir. Paris. Anesthesie 1980;36840 E10, 10-1980.

2. Traynor C, Hall GM. Endocrine and metabolic changes during surgery: anaesthetic implications. Br J Anaesth 1981;53:153-60.

3. Moller IW, Rem J, Brandt MR, Kehlet H. Effect of posttraumatic epidural analgesia on the cortisol and hyperglycaemic response to surgery. Acta Anaesthesiol Scand 1980;26:56-8.

4. Kehlet H. Influence of epidural analgesia on the endocrine-metabolic response to surgery. Acta Anaesthesiol Scand 1978; 70(Suppl):39-42.

5. Kehlet H. Epidural analgesia and the endocrine metabolic response to surgery. Update and perspectives. Acta Anaesthesiol Scand 1984;28:125-7.

6. Engquist A, Brandt MR, Fernandes A, Kehlet H. The blocking effect of epidural analgesia on the adrenocortical and hyperglycemic responses to surgery. Acta Anaesthesiol Scand 1977; 21:330-5.

7. Jensen CH, Berthesen P, Kühl C, Kehlet H. Effect of epidural analgesia on glucose tolerance during surgery. Acta Anaesthesiol Scand 1980;24:472-4.

8. Brandt MR, Fernandes A, Mordhorst R, Kehlet H. Epidural analgesia improves postoperative nitrogen balance. Br Med J 1978;1:1106-8.

9. Renck H. The elderly patient after anaesthia and surgery with special regard to certain respiratory circulatory metabolic and muscular functions. Acta Anaesthesiol Scand suppl 1969; 46:13-58.

10. Hakanson E, Rutberg H, Jorfeld L, Martensson J. Effects of the extradural administration of morphine or bupivacaine on the metabolic response to upper abdominal surgery. Br J Anaesth 1985;57:394-9.

11. Hjortso NC, Christensen NJ, Andersen J, Kehlet H. Effects of the extradural administration of local anaesthetic agents and morphine on the urinary excretion of cortisol, catecholamines and nitrogen following abdominal surgery. Br J Anaesth 1985; 57:400-6.

12. Delalande JP, Le Page JL, Perramant M, Lozac'h P, Tanguy RL. Influence de l'anesthésie péridurale sur l'épargne azotée post-opératoire en chirurgie viscérale majeure. Ann Fr Anesth Réanim 1984;3:16-21.

13. Tsuji H, Shirasaka C, Asoh T, Uchida I. Effect of epidural administration of local anesthetics or morphine on postoperative nitrogen loss and catabolic hormones. Br J Surg 1987; 74:421-6.

14. Bromage PR. Ageing and epidural dose requirements segmentals spread and predictability of epidural analgesia in youth and extreme age. Br Med J 1969;41:1016-8.

15. Patricot MC, Mathian B, Heyries D, Revol D. Dosage de la 3-méthyl-histidine urinaire par chromatographie en phase gazeuse: signification des valeurs usuelles chez l'adulte. Ann Biol Clin 1983;41:213-7.

16. Alper CA. Plasma protein measurements as a diagnostic aid. N Engl J Med 1974;291:287-90.

17. Jorgensen BC, Andersen HB, Enguist A. Influence of epidural morphine on postoperative pain, endocrine metabolic, and renal responses to surgery. A controlled study. Acta Anaesthesiol Scand 1982;26:63-8.

18. Rutberg H, Hakanson E, Anderberg B, Jorfeld L, Martensson J, Schild B. Effects of morphine, or bupivacaine, on the endocrine response to surgery. Br J Anaesth 1984;56:233-8.

19. Tallen H, Stein WH. 3MH: a new amino acid from human urine. J Biol Chem 1954;206:825-34.

20. Long CL, Haverberg LN, Young VR, Kinney JM, Munro HN, Geiger JW. Metabolism of 3-methylhistidine in man. Metabolism 1975;24:929-31.

21. Ballard FJ, Tomas FM. 3-Methylhistidine as a measure of skeletal muscle protein breakdown in human subjects: the case for its continued use. Clin Sci 1983;65:209-15.

22. Rennie MJ, Bennegard K, Eden E, Emery PW, Lundholm K. Urinary excretion and efflux from the leg of 3-methylhistidine before and after major surgical operation. Metabolism 1984; 33:250-6.

23. Millward DJ, Bates PC. Quantitative importance of non-skeletal sources of 3 MH. Biochem J 1980;190:225-8.

24. Nishizawa N, Nogushi T. Fractionnel flux rates of 3 MH in skin and gastro-intestine: the contribution of these tissues to urinary excretion of 3 MH in the rate. Br J Nutr 1977;38:149-52.

25. Gross E, Holbrook IB, Irving MH. The effect of elective surgery on 3-methylhistidine excretion. Br J Surg 1978;65:663-5.

26. Christensen P, Brandt MR, Rem J, Kehlet H. Influence of extradural morphine on the adrenocortical and hyperglycaemic response to surgery. Br J Anaesth 1982;54:23-7.

27. François G, Blanc M, Blache JL, Granthil C, Rose F. Interêt du dosage de la 3-méthylhistidine (3Méhis) urinaire dans l'évaluation du catabolisme musculaire post opératoire. Ann Anesth Franç 1981;4:339-45.

28. Neuhäuser M, Bergström J, Chao L, Holmström B, Nordlund L, Vinnars E, Fürst P. Urinary excretion of 3-methylhistidine as an index of muscle protein catabolism in postoperative trauma: the effect of parenteral nutrition. Metabolism 1980;29:1206-13.

Effects of Thoracic Epidural Anesthesia on Systemic Hemodynamic Function and Systemic Oxygen Supply-Demand Relationship

K. Reinhart, MD, U. Foehring, MD, T. Kersting, MD, M. Schaefer, MD, D. Bredle, PhD, A. Hirner, MD, and K. Eyrich, MD

REINHART K, FOEHRING U, KERSTING T, SCHAEFER M, BREDLE D, HIRNER A, EYRICH K. Effects of thoracic epidural anesthesia on systemic hemodynamic function and systemic oxygen supply-demand relationship. Anesth Analg 1989;69:360–9.

The effects of thoracic epidural anesthesia (TEA) on total body oxygen supply-demand ratio are complex due to potential influences on both O_2 delivery ($\dot{Q}O_2$) and consumption ($\dot{V}O_2$). One hundred and five patients undergoing abdominal aortic surgery were randomly assigned to one of three groups to compare the cardiovascular and metabolic responses associated with (1) thoracic epidural anesthesia plus light general anesthesia (group TEA); (2) general anesthesia with halothane (group H); and (3) neuroleptanalgesia (group NLA). Values of cardiac index (CI) and $\dot{Q}O_2$ were less intraoperatively in the TEA group than in the H or NLA groups, while $\dot{V}O_2$ values were similar. $\dot{V}O_2$ during recovery was greater in both the TEA and NLA groups than in the H group. Consequently the oxygen supply-demand ratio ($\dot{Q}O_2/\dot{V}O_2$) was less in the TEA group throughout the perioperative period and about 30% below baseline values during early recovery. At comparable $\dot{V}O_2$, CI and mixed venous O_2 saturation were always less in the TEA group than in the NLA group. Heart rate was slowest intraoperatively during TEA, and stroke work was less with TEA than with NLA. As cardiac filling pressure and systemic vascular resistance did not differ among the three groups, reduced adaptation of CI to tissue O_2 needs during TEA was attributed to negative inotropic and chronotropic effects of the sympathetic blockade. We conclude that in patients undergoing abdominal aortic surgery, TEA has no apparent advantage over general anesthesia.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. OXYGEN, SUPPLY/DEMAND RATIO—epidural anesthesia.

Thoracic epidural anesthesia (TEA), alone or in combination with light general anesthesia, has been advocated for cardiac risk patients undergoing major surgery (1–3). Beneficial effects of TEA have been described both in human beings and in animal models (2,4). For example, coronary vasoconstriction was limited by blockade of either sympathetic efferents to the heart or afferents from the surgical field during painful stimuli (2). On the other hand, marked cardiovascular depression by epidural anesthesia alone

or in combination with general anesthesia has been reported (5–8). This has been attributed to a reduction in peripheral vascular resistance secondary to diminished sympathetic tone and a decrease in venous return to the heart (9). If upper thoracic segments (T_1–T_5) are involved in the block, sympathetic outflow to the heart is decreased. This might contribute to a reduction of cardiac output (5,10,11) with a subsequent decrease in total systemic oxygen (O_2) delivery. However, total O_2 consumption during and after TEA might also be reduced due to diminished sympathetic tone, as catecholamines play an important role in setting the metabolic rate (12). Oxygen consumption ($\dot{V}O_2$) levels immediately after surgery have been reported to be lower during regional than during general anesthesia (13). Thus, the oxygen supply-demand ratio could increase, decrease, or remain unchanged.

Yeager et al. (3), in comparing epidural with general anesthesia, found significant reductions in the

Table 1. Preoperative Characteristics and Duration of Surgery within the Three Study Groups

	Anesthesia		
	H	NLA	TEA
Number of Patients	30	40	35
Gender (M/F)	22/8	30/10	25/10
Age (yr)	61 ± 11	60 ± 10	63 ± 11
BSA (m²)	1.81 ± 0.17	1.82 ± 0.14	1.78 ± 0.16
ASA-status			
I	1	0	1
II	11	16	12
III	18	24	22
Duration of Surgery (min)	229 ± 74	238 ± 87	234 ± 92

H = halothane, NLA = neuroleptanalgesia, TEA = thoracic epidural analgesia, BSA = body surface area. All values are mean ± SD.

overall complication rate and the incidence of cardiovascular failure with epidural anesthesia. Other studies, however, could not demonstrate major beneficial effects of epidural anesthesia as compared to general anesthesia with respect to postoperative morbidity and mortality (14,15). The present study was designed to test the hypothesis that TEA, compared with general anesthesia, is associated with beneficial effects on systemic hemodynamic function and the oxygen supply-demand relationship in patients undergoing aortic surgery.

Methods

In a randomized prospective study 105 patients, ASA physical status mostly 2–3, scheduled for elective abdominal aortic surgery due to occlusive disease (N = 82) or aneurysm (N = 23), were randomly assigned to one of the three following groups:

Group H (N = 30) : halothane (0.8–1.2 Vol%) was administered in a mixture of nitrous oxide (N₂O) and O₂ (2:1).

Group NLA (N = 40) : neuroleptanalgesia with fentanyl (25–30 μg/kg) in combination with droperidol (15–25 mg) and N₂O/O₂ (2:1).

Group TEA (N = 35) : thoracic epidural anesthesia with sensory blockade at levels between T_{3-5} and L_{2-3} in combination with light general anesthesia with diazepam (20–25 mg) and N₂O/O₂ (2:1).

No differences in patient characteristics were noted among the three groups (Table 1). The different number of patients in the groups resulted from the fact that lactate and pyruvate determinations were

not begun until patient #45. Unequal group size at that point meant that a new randomization was necessary for assigning the subsequent 60 patients. The study was approved by our institutional human investigation committee, and written informed consent was obtained from all subjects.

Premedication

Patients in all groups were premedicated with oral diazepam (10 mg) the night before surgery and with meperidine (1 mg/kg, to a maximum of 75 mg), as well as 50 mg promethazine and 0.5 mg atropine intramuscularly approximately 1 hr before surgery. Thirty minutes after premedication the right or left radial artery was catheterized percutaneously for direct blood pressure measurement and blood sampling. A thermistor tipped Swan-Ganz catheter (Model 93A-837-77.5 VIP) was inserted into a pulmonary artery via the right internal jugular vein under local anesthesia. TEA patients had a 22-gauge epidural catheter inserted through the T_{7-8} or T_{8-9} intervertebral space with the aid of a 16-gauge Tuohy needle. After a test dose of 3 mL bupivacaine 0.5% (without epinephrine), an additional 6–10 mL was injected. The distribution of the sensory block was determined in 25–30 min. The TEA-induced level of sensory loss extended in a cephalad direction to T_3 and T_5 and caudally to between L_2 and L_3.

General anesthesia was induced in all groups with thiopental (3–5 mg/kg). Pancuronium (1–2 mg) and succinylcholine (1–2 mg/kg) were administered to facilitate tracheal intubation in all patients. Controlled ventilation with a mixture of N₂O and O₂ (2:1) was provided to maintain arterial P_{CO_2} at 35–40 mm Hg as continuously measured in end-tidal air.

The NLA patients received fentanyl (0.3–0.5 mg, IV) before induction of anesthesia and intubation, and droperidol (10–15 mg) after intubation. Another 0.2 mg fentanyl was given before skin incision followed by repeated doses of 0.1–0.2 mg every 30 min or at any signs of insufficient analgesia (increase in heart rate or blood pressure more than 10–15%, or sweating). Half of the initial dose of droperidol was repeated after 2 hr. For intraoperative relaxation, pancuronium (0.1 mg/kg) was administered at the beginning of surgery and additionally as needed.

In group H patients, halothane was titrated to maintain mean arterial blood pressure between 75 and 90 mm Hg. Relaxation was achieved in the same way as for the NLA patients.

In order to tolerate intubation and ventilation, TEA patients were given diazepam during surgery by

Table 2. Drugs Used for Relaxation and Anesthesia

	Anesthesia		
Drugs	H	NLA	TEA
Pancuronium (mg)	7.25 ± 3.3	9.55 ± 4.7	5.7 ± 4.0
Fentanyl (mg)	—	1.9 ± 0.7	—
Droperidol (mg)	—	22.2 ± 11.4	—
Diazepam (mg)	—	—	21.8 ± 6.8
Bupivacaine 5% (mg)	—	—	155 ± 22

For abbreviations, see footnote to Table 1. All values are mean ± SD.

Table 3. Study Stages

1) Baseline
2) 3–5 min after intubation
3) 3–5 min after skin incision
4) 3–5 min before aortic clamping
5) 3–5 min after aortic clamping
6) 3–5 min before aortic declamping
7) 3–5 min after aortic declamping
8) End of surgery
9) Arrival at the ICU
10) 1 hr after arrival at the ICU
11) 2 hr after arrival at the ICU
12) 8 hr after arrival at the ICU
13) 24 hr after end of surgery

continuous infusion (10 mg in 500 mL NaCl, 250 mL/h). Half the initial dose of bupivacaine was given every 90 min. Pancuronium (0.05 mg/kg) was also administered to these patients after intubation and additionally as needed. A summary of the amount of drugs used for anesthesia and relaxation is presented in Table 2.

Crystalloids, colloids, and blood were administered intraoperatively in all three groups to maintain pulmonary capillary wedge pressure (PCWP) at 10–12 mm Hg. Before aortic declamping PCWP was increased to 15–18 mm Hg by rapid infusion of blood or colloids. Blood was transfused to maintain hemoglobin values above 10 g/dL. Hydroxyethylstarch 10% (HES) (max. 1000 mL) and albumin 20% (max. 100 mL) were used as colloids. If mean arterial pressure (MAP) decreased below 50 mm Hg during anesthesia despite PCWP >15 mm Hg, and if it could not be corrected by decreasing the depth of anesthesia, dopamine or norepinephrine was given to increase MAP above 75 mm Hg. Dopamine was selected if cardiac output (CO) was considered to be relatively small as indicated by mixed venous O_2 saturation ($S\bar{v}_{O_2}$) <70%. If $S\bar{v}_{O_2}$ was larger than 70%, norepinephrine was infused. The beta-adrenoceptor antagonist acebutolol was administered in doses of 2.5 to 5 mg to control hypertension if heart rate exceeded 95 beats/min and/or if rate pressure product (RPP) exceeded 18,000. If RPP exceeded 18,000 but heart rate was <95, nitroglycerin (NTG) was administered.

At the end of surgery, N_2O was discontinued in all groups as well as halothane in group H, and the patients were transferred to the ICU for postoperative monitoring and care. All patients were mechanically ventilated until they became normothermic. Patients were sedated with diazepam as needed IV. Tracheas were extubated when the patients had adequate spontaneous breathing and normal blood gas tensions. Dihydralazine, alone or in combination with NTG and acebutolol, was used for treatment of postoperative hypertension. Piritramide was used for pain control in the NLA and H patients, whereas in TEA patients bupivacaine 0.25% was administered

epidurally for postoperative pain control in amounts adequate to keep the sensory block above T_{5-6}.

Monitoring and Measurement Procedures

Heart rate, electrocardiogram (lead V_5), systemic arterial pressure, pulmonary artery pressure, central venous pressure, and end-tidal CO_2 fraction (Hewlett Packard Model 47210) were continuously recorded on a Hewlett Packard 8 channel recorder (Model 7758 A). CO was determined in triplicate using the thermodilution technique. Core body temperature was monitored by the thermistor probe of the Swan-Ganz catheter. Measurements were obtained during 13 study stages through the perioperative period (Table 3). At each study stage, standard hemodynamic data were recorded; arterial and mixed venous blood samples were withdrawn simultaneously for measurements of P_{O_2}, P_{CO_2}, pH, and base excess (ABL 2 Radiometer, Copenhagen). Hemoglobin content and oxygen saturation were measured with an IL 282 Co-oximeter. In 60 patients samples for lactate and pyruvate determinations were taken from the pulmonary artery. The samples were immediately denatured with perchloric acid and cooled on ice. Lactate and pyruvate determinations were completed within 4–6 hr by enzymatic UV test according to methods described by Noll (16) and Czok (17) using test kits (Boehringer, Mannheim, Germany). Excess lactate, defined as the arterial lactate corrected for the concomitant changes in pyruvate unrelated to tissue hypoxia, was calculated according to Huckabee (18).

The hemodynamic and oxygen transport variables were derived according to standard formula (19). Oxygen content in arterial (Ca_{O_2}) and in mixed venous blood was derived from measured hemoglobin concentration, O_2 saturation, and P_{O_2}. Oxygen delivery ($\dot{Q}_{O_2}$) was calculated as cardiac index (CI) times Ca_{O_2}. $\dot{V}_{O_2}$ was calculated using the Fick prin-
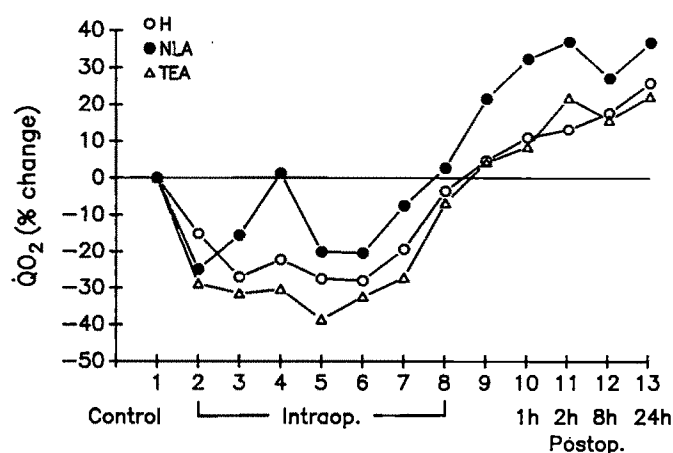
Figure 1. Oxygen delivery in each group at each of the 13 study stages expressed as percent change from baseline levels. H = halothane, NLA = neuroleptanalgesia, TEA = thoracic epidural analgesia.

Figure 2. Oxygen consumption in each group at each of the 13 study stages expressed as percent change from baseline levels.

ciple as the product of CI and arteriovenous oxygen content difference ($avDO_2$).

Statistical analyses for comparison between experimental groups were made with a Kruskal-Wallis H-Test and a post-hoc Mann-Whitney U-test (20). Within-group differences were tested with a Wilcoxon signed-rank test. Nonparametric analyses were made because some of the variables did not have the normal distribution required for parametric tests. Statistical significance was accepted at $P < 0.05$.

Figure 3. Oxygen supply to demand relationship in each group at each of the 13 study stages expressed as percent change from baseline levels.

Results

Similar amounts of crystalloids, colloids, and blood were given intraoperatively in the three groups. Mean core temperature decreased similarly in all three groups: 35.1 ± 1.4°C (NLA), 34.1 ± 1.0°C (H), and 34.6 ± 1.2°C (TEA). Postoperative extubation time was 4.7 ± 2.2 hr (NLA), 2.0 ± 1.9 hr (H), and 2.7 ± 2.3 hr (TEA), without significant differences among the groups.

Oxygen transport related variables for the 13 study stages are shown in Figures 1–5 as percent change from baseline. The hemodynamic and metabolic data, with significant between- and within-group differences identified, are provided in Tables 4 and 5. MAP and left ventricular stroke work index (Table 5) were similar in TEA and H patients but were significantly smaller than in NLA patients intraoperatively and up to 1 hr postoperatively. Rate pressure products above 12,000 were seen in 9.3% of the measurements in TEA patients compared to 12.2% in H and 17.1% in NLA patients, without significant differences among the groups (Table 5). CI was significantly less at five intraoperative and two postoperative study stages in

TEA compared to NLA (Figure 5 and Table 5). $\dot{Q}O_2$ was significantly less in group TEA than in group NLA at four intraoperative and three postoperative study stages (Figure 1, Table 4). $\dot{V}O_2$ was similar in these two groups during all stages (Figure 2). In contrast to groups H and NLA, oxygen supply-demand ratio ($\dot{Q}O_2/\dot{V}O_2$) decreased during TEA after induction of anesthesia, and early in recovery it was reduced as much as 30% below baseline levels (Figure 3). TEA patients had significantly larger $avDO_2$ (Table 4) and smaller $S\bar{v}_{O_2}$ levels (Figure 4 and Table 4) than did patients in the other two groups at several study stages, differences that became greatest in the early postoperative period. Figure 6 shows that over the range of $\dot{V}O_2$ observed during the perioperative period, from 40 to 250 mL/min/m², $S\bar{v}_{O_2}$ and CI were always lower in group TEA than in group NLA for a similar $\dot{V}O_2$. Excess lactate concentrations did not increase above 1 mmol/L in any of the groups (Table 4).
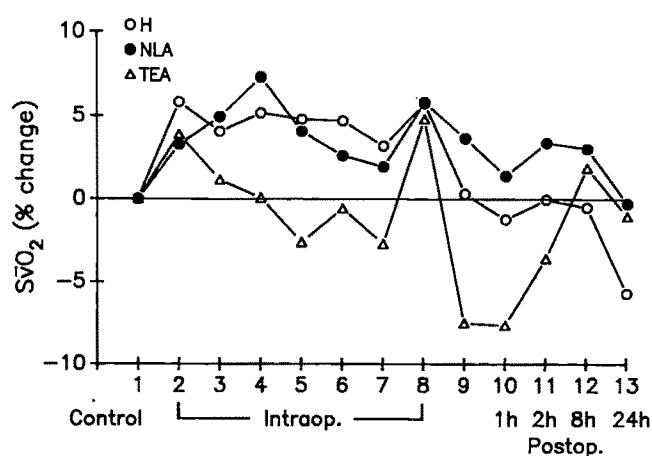
Figure 4. Mixed venous oxygen saturation in each group at each of the 13 study stages expressed as percent change from baseline levels.
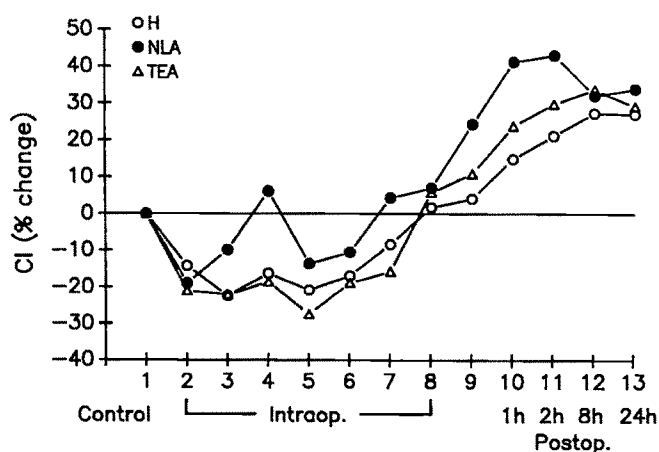
Figure 5. Cardiac index in each group at each of the 13 study stages expressed as percent change from baseline levels.

Discussion

Oxygen Supply-Demand Ratio

$\dot{V}O_2$ decreased similarly during surgery in all three groups in accordance with the findings of others (21–24). The slower increase of $\dot{V}O_2$ in group H after discontinuation of halothane, which is known to depress sympathetic activity (25), might result from the relatively slow wash-out of halothane from the body (26). Renck (13) found an increase in $\dot{V}O_2$ after 15 min of urological surgery with spinal and epidural analgesia that was less than that observed at the same time in patients given halothane and barbiturate anesthesia. Renck attributed this to the complete absence of pain with the regional anesthesia. However, pain should not have been a factor in our postoperative period because TEA and sedation were continued in the ICU, and the other two groups were sedated and received analgesics intravenously. The

similarity in $\dot{V}O_2$ levels in groups TEA and NLA in our study during awakening and rewarming indicates that blockade of peripheral afferent and efferent fibers with bupivacaine was without major effect on metabolism. In contrast, β adrenergic receptor antagonists are able to suppress the calorigenic effect of increased sympathetic tone and its corresponding increase in $\dot{V}O_2$ (27). This difference might be explained by the fact that blockade of the nervous pathways by epidural anesthesia usually is not complete; partially blocked and unblocked fibers can be recruited, depending on the central sympathetic tone (28).

A major finding of this study was that $\dot{Q}O_2$ was generally less during TEA than during H or NLA. Arterial O_2 content did not differ among the three groups (Table 5), but CI was less with TEA. Tissue need for oxygen is an important factor in regulation of CO (29); a decrease in CI can therefore reflect either a decrease in oxygen requirements or a relative inadequacy of CI. The intraoperative decrease in $\dot{V}O_2$ and CI in the TEA group was accompanied by a lower $S\bar{v}_{O_2}$ than in the other two groups, in which $S\bar{v}_{O_2}$ was increased above baseline. With increasing $\dot{V}O_2$ in the early postoperative period, this decrease in $S\bar{v}_{O_2}$ in group TEA was most pronounced. Apparently, the reduction in $S\bar{v}_{O_2}$ resulted from an increase in oxygen extraction reflecting relative inadequacy of CI. In the TEA group the postoperative increase in $\dot{V}O_2$ (150% of baseline) was associated with an increase in O_2 extraction, whereas in the NLA group a similar increase in $\dot{V}O_2$ was due primarily to an increase in CI. Thus, when $\dot{Q}O_2$ and $\dot{V}O_2$ are considered together, the matching of CI to tissue O_2 needs was poorest with TEA (Figures 3 and 6). In this study in all three groups, however, $\dot{Q}O_2$ was not impaired to the degree that significant excess lactate production occurred (Table 4).

Cardiovascular Effects of TEA

Differences in preload, afterload, heart rate, or contractility could have accounted for the relatively smaller CI in TEA. Fluid volume replacement kept CVP and PCWP within the upper range of normal, and there were no intergroup differences in these factors. Systemic vascular resistance, which accounts for over 90% of output impedance for the left ventricle (30), differed very little among the groups (Table 5). Effects on ventricular contractility and/or heart rate, therefore, were apparently responsible for the relatively smaller CI during group TEA at any given degree of oxygen consumption (Figure 6). Heart rate

Table 4. Variables Related to Oxygen Transport

| | Study Stages | | | | | | | | | | | |
	1	2	3	4	5	6	7	8	9	10	11	12	13
$\dot{Q}O_2$ (mL·min⁻¹·m⁻²)													
H	546*	463*	398	424*	396	393	440	526	571	606	618	643	687
	±130	±119	±131	±95	±96	±104	±93	±137	±179	±181	±230	±191	±171
NLA	537*	403	454	544*	429	428	497	552	653	711	736	684	736
	±169	±134	±147	±158	±133	±101	±173	±144	±171	±160	±137	±198	±103
TEA	547*	389	374	381*	335	370	398	510	570	593	666	633	669
	±127	±177	±127	±121	±120	±127	±121	±118	±183	±109	±144	±182	±136
		α,β	γ	β,γ	α,γ		γ		β,γ	β,γ	β,γ		
$\dot{V}O_2$ (mL·min⁻¹·m⁻²)													
H	122*	84	81	83	77	75*	90	96*	122	134	140	135	168
	±33	±24	±22	±19	±20	±19	±24	±31	±58	±49	±52	±29	±30
NLA	115*	83	86	96	85	94*	107	104*	142	178	151	148	167
	±28	±18	±24	±26	±20	±24	±35	±21	±67	±66	±41	±41	±26
TEA	118*	83	85	85	80	85	94	105*	151	179	185*	144	159
	±22	±17	±22	±19	±15	±19	±24	±34	±56	±60	±71	±38	±30
				β		α,β	β		α	α,β	α		
$\dot{Q}O_2/\dot{V}O_2$													
H	4.6	5.1	4.9	5.2	5.1	5.0	5.1	3.7*	4.7	4.4	4.5	4.9	4.1
	±1.2	±1.3	±1.1	±1.1	±1.2	±1.2	±1.5	±2.0	±1.2	±1.1	±1.0	±1.7	±.8
NLA	4.5	4.4	5.1	5.7*	4.9	4.6	4.6	5.1	4.8	4.5	4.9	4.8	4.8
	±.9	±1.0	±1.9	±1.8	±1.1	±1.1	±1.6	±1.0	±1.3	±1.4	±1.3	±1.1	±1.5
TEA	4.5	4.5	4.3	4.4	4.2	4.0	4.2	5.4	3.7	3.4*	4.0	4.6	4.3
	±.8	±1.0	±1.0	±1.3	±1.6	±.9	±1.3	±2.1	±1.1	±.5	±.9	±1.4	±.8
		β,γ	γ	α,γ	α,γ	γ	γ		α,γ	α,γ	α		
avDO₂ (mL/dL)													
H	3.6*	3.0	2.9	2.9	2.8	3.0	3.1	2.8*	3.4	3.5	3.5	3.4	3.9
	±.9	±.6	±.5	±.7	±.5	±.5	±.8	±.7	±1.1	±.9	±.8	±.8	±.7
NLA	3.5*	3.2	3.3	2.9	2.9	3.1	3.2	2.8	3.2	3.8*	3.2	3.3	3.5
	±.7	±.7	±1.0	±.6	±.6	±.8	±.8	±.6	±1.0	±1.1	±.8	±.9	±.5
TEA	3.7*	3.3	3.5	3.5	3.8	3.4	3.7	3.2*	4.3	4.5	3.9*	3.5	3.7
	±.8	±.9	±.8	±.9	±1.4	±.7	±1.0	±1.0	±1.4	±.9	±1.1	±.7	±.7
			α	α,γ	α,γ	α	α			α,γ	α,γ	γ	β
$S\bar{v}_{O_2}$ (%)													
H	73*	78	76	77	77	77	76	78*	74	73	74	73	69
	±8	±8	±5	±8	±4	±5	±8	±8	±7	±7	±8	±8	±7
NLA	73*	75	77	78*	76	75	74	77	76	74	75	75	72
	±4	±5	±7	±8	±8	±5	±8	±4	±8	±7	±7	±5	±4
TEA	72*	75	73	73	71	72	70	76*	67	67	70*	74	72
	±4	±5	±5	±8	±10	±5	±7	±7	±8	±5	±8	±8	±4
	α,β	α		α,γ	α,γ	α	α		α,γ	α,γ	γ		
CaO₂ (mL/dL)													
H	16.5*	15.5*	14.7*	14.6	14.2	13.7	13.9	14.7*	15.3	15.1	15.4	15.5	15.7
	±2.4	±2.4	±2.5	±2.3	±2.2	±1.8	±1.8	±2.0	±2.0	±1.8	±1.9	±1.9	±1.9
NLA	15.8*	14.3	14.3	14.4	14.3	13.8	13.8	14.9*	15.4*	16.0*	15.2	15.4	16.0
	±1.9	±2.2	±1.9	±2.4	±1.6	±1.6	±1.2	±1.6	±1.1	±1.2	±1.6	±2.3	±1.6
TEA	16.5*	14.6	14.4	14.0	13.9	13.4	13.9	14.8	15.3	15.4	15.4	15.8	16.0
	±1.9	±2.0	±2.5	±2.2	±2.4	±2.2	±1.9	±1.7	±2.0	±1.7	±1.9	±1.9	±1.7
										β			
EL (mmol/L)													
H		.21		.33	*	.88	.95	.97	.68	.40	.75		
		±.29		±.32		±.69	±.55	±.90	±.84	±.96	±1.44		
NLA		.03	*	.29		.43	.64*	.58	.55	.63*	.14		
		±.37		±.48		±.73	±.99	±1.04	±.82	±.92	±.77		
TEA		.08		.27		.34*	.93	.75*	.28	.34	.42		
		±.39		±.41		±.76	±1.02	±.97	±.73	±.66	±.96		
						β							

Values are mean ± SD. Group abbreviations: H = halothane; TEA = thoracic epidural anesthesia; NLA = neuroleptanalgesia. $\dot{Q}O_2$ = O_2 delivery; $\dot{V}O_2$ = O_2 consumption; $\dot{Q}O_2/\dot{V}O_2$ = O_2 supply to demand ratio; avDO₂ = arterio venous O_2 content difference; $S\bar{v}_{O_2}$ = mixed venous O_2 saturation; CaO₂ = arterial O_2 content; EL = excess lactate. Significant intergroup differences ($P < 0.05$) are denoted by α = TEA vs H; β = H vs NLA; γ = TEA vs NLA.
* = $P < 0.05$ between consecutive measurements.

Table 5. Hemodynamic Variables

						Study Stages							
	1	2	3	4	5	6	7	8	9	10	11	12	13
MAP (mm Hg)													
H	105	99	92	85*	91	88*	78	86*	103	91	92	86	84
	±18	±21	±20	±17	±18	±13	±11	±14	±25	±16	±18	±11	±19
NLA	100*	76*	93	97	99	99	90	97*	120*	92	87	81	88
	±18	±17	±20	±20	±18	±16	±16	±18	±22	±15	±13	±11	±12
TEA	97*	80	76	79	84	90*	76	80*	89*	97	92	81	92
	±15	±16	±16	±17	±16	±11	±15	±18	±19	±18	±18	±16	±19
	α,β	α,γ	β,γ	γ	β,γ	β,γ	β,γ	β,γ					
HR (b/min)													
H	84*	94*	84	84	83	83	85	83	85	84*	90	94	98
	±19	±15	±21	±17	±15	±16	±16	±16	±20	±18	±16	±16	±15
NLA	80	76	77	85*	80	72*	81	79*	92*	102	103	94	96
	±15	±17	±16	±20	±17	±15	±18	±16	±19	±20	±15	±15	±19
TEA	84*	74	71	74*	69	71	73	73	77*	88*	89	93	93
	±18	±16	±17	±15	±16	±15	±15	±15	±17	±20	±20	±15	±18
	α,β	α	α,γ	α,γ	α,β	α	α	γ	β,γ	β,γ			
PCWP (mm Hg)													
H	7*	12	14	11*	12	16	15	14*	10	10	10	9	9
	±3	±4	±5	±4	±4	±4	±5	±3	±4	±3	±4	±2	±5
NLA	7*	10	12	12	12	15	13	12	10	9	9*	10	8
	±3	±4	±4	±5	±4	±5	±4	±4	±5	±4	±3	±4	±2
TEA	7*	10	11	11	11	14	12	14	10	11	10	9	9
	±3	±3	±3	±4	±4	±5	±4	±5	±5*	±4	±4	±4	±5
	β	α,γ						β				β	
CI (L·min⁻¹·m⁻²)													
H	3.4*	2.9*	2.7	2.9	2.7	2.9	3.2	3.5	3.6*	4.0	4.2	4.4	4.4
	±.7	±.6	±.7	±.6	±.6	±.7	±.7	±.8	±.9	±1.0	±1.1	±1.3	±.9
NLA	3.4*	2.8	3.1	3.6*	2.9	3.1*	3.6	3.7*	4.2*	4.9	4.9	4.5	4.6
	±1.0	±.8	±.9	±1.0	±.8	±.7	±1.4	±.9	±1.3	±1.2	±1.2	±1.1	±.8
TEA	3.3*	2.6	2.6	2.7*	2.4	2.7	2.8	3.5	3.7	4.1*	4.3	4.4	4.2
	±.7	±.7	±.7	±.8	±.8	±.7	±.8	±.9	±.9	±1.0	±1.0	±1.0	±.9
	γ	β,γ		γ	γ		α,γ		β,α	β,γ	β		γ
LVSWI (g·min⁻¹·m⁻²)													
H	56*	37*	33	34	35	36	34	41*	58	54	51	51	49
	±16	±10	±9	±7	±9	±10	±7	±10	±16	±12	±16	±14	±16
NLA	54*	35*	46	50	47	51	49	56*	74*	54	51	50	52
	±15	±9	±16	±16	±17	±16	±17	±21	±18	±15	±15	±15	±11
TEA	49*	37	36	36	38	40	35*	43*	52	54	56*	45	53
	±14	±10	±11	±8	±10	±9	±11	±11	±15	±17	±15	±13	±13
	β,γ	β,γ	β,γ	α,β,γ	β,γ	β,γ	β,γ						
SVR (dyne·cm⁻⁵·m⁻²)													
H	1284	1343	1304	1128*	1295	1218*	993	1048*	1206*	1058	993	855	844
	±249	±348	±319	±285	±324	±346	±213	±297	±364	±315	±407	±261	±266
NLA	1212*	1055*	1157	1080	1310	1302	1094	1104	1222*	823	796	767	803
	±264	±266	±346	±367	±324	±289	±386	±299	±389	±259	±251	±254	±207
TEA	1271	1137	1159	1167*	1287	1305*	1126	939	1092	1078*	957	842	930
	±281	±344	±248	±315	±288	±350	±385	±311	±342	±299	±309	±249	±267
		β								β,γ	γ		
RPP (mm Hg/min²)													
H	14034	14218*	11620	10808	11492	11189*	9905	11031*	14477	14039	15049	14747	14561
	±4011	±5005	±4547	±3972	±4446	±3841	±2913	±3386	±5517	±4913	±4331	±4365	±4981
NLA	13550*	8873*	10708	12476	12734	11482	11742	12747	18549	15998	16549	13634	14647
	±4010	±2978	±3096	±4137	±4130	±3642	±3824	±4207	±5331	±4083	±4249	±3389	±4065
TEA	12879*	8948	8311	9110	9111	9988*	8597	9543*	11388*	13651*	14819	13819	14806
	±3935	±2695	±3199	±3456	±3489	±3012	±3057	±3682	±4652	±3653	±4254	±3808	±3877
	α,β	α,γ	γ	α,γ			β,γ	γ	α,β,γ	β,γ			

Values are mean ± SD. Group abbreviations are the same as in Table 5. MAP = mean arterial pressure; HR = heart rate; PCWP = pulmonary capillary wedge pressure, CI = cardiac index; LVSWI = left ventricular stroke work index; SVR = systemic vascular resistance; RPP = rate pressure product. Significant intergroup difference ($P < 0.05$) are denoted by α = TEA vs H; β = H vs NLA; γ = TEA vs NLA.
*$P < 0.05$ between consecutive measurements.
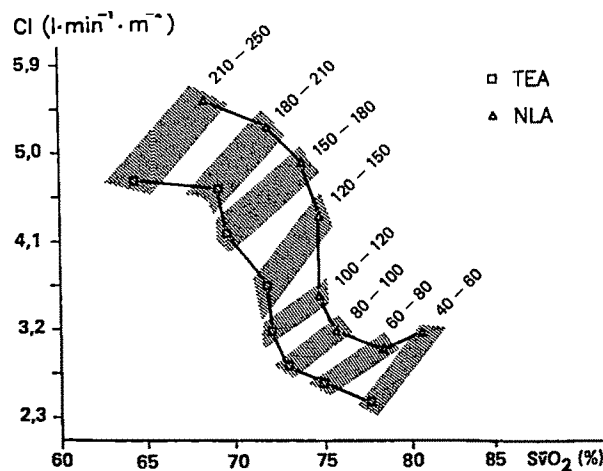
Figure 6. Relationship between cardiac index and mixed venous O₂ saturation over the range of oxygen consumptions observed during the perioperative period during thoracic epidural analgesia and during neuroleptanalgesia. VO_2 values (mL/min/m²) in the two groups are indicated by the numbers beside each shaded area.

was indeed slower during TEA than in the other two groups (Table 5). Depression of baroreflex activity has been reported with lumbar epidural anesthesia, even without blockade of sympathetic efferents to the heart, due to enhanced vagal tone (31). Our data suggest that not only a decrease in heart rate but also a decrease in contractility could be responsible for CI reduction during TEA. Stroke work index decreased to a similar degree during TEA and halothane, a known negative inotropic drug (32). Potential mechanisms for reduced contractility with spinal as well as epidural anesthesia include diminished adrenal medullary release of catecholamines and reduced sympathetic outflow to the heart when the blockade involves the upper five thoracic segments (28). In addition, central sympathetic drive is reduced by premedication and general anesthesia (33). These factors may all have contributed to the smaller CI observed in the TEA patients. Other studies have likewise shown smaller CI intraoperatively with the combination of TEA and light general anesthesia compared to general anesthesia alone (10,11). Using thoracic epidural block (T_1–T_{12}) in combination with general anesthesia for major vascular surgery, Reiz et al. (5) had to administer constant infusion of the β-adrenoceptor agonist prenalterol since the epidural block alone decreased CI by 0.5 L/min and MAP by 40 mm Hg.

An increase in sympathetic tone plays an important compensatory role in cardiac failure (34–36), and patients with cardiac insufficiency often exhibit increased O₂ extraction ratio even at rest (37,38). A reduction of sympathetic drive is consistent with our

observations of reduced oxygen delivery and increased O₂ extraction with TEA.

Similarly, in models of limited $\dot{Q}O_2$ due to hypoxia, anemia, or acute blood loss the role of sympathetic drive was shown to be important (39–41). The use of TEA, therefore, may not be beneficial to patients with compromised O₂ supply-demand ratio. However, in patients with coronary artery disease without impaired cardiac performance, TEA may offer some advantages since lower heart rate and reduced contractility might reduce the myocardial O₂ demand. The vasoactive drugs used at least one time in approximately one-third of patients in this study could have affected both O₂ transport and hemodynamic variables. However, the number of subjects given vasoactive drugs was similar in all three groups, and, when analyzed without these patients, the data revealed the same statistical differences. We feel, therefore, that the administration of these drugs did not confound the specific effects of the anesthesia.

Clinical Implications

Hospital mortality and postoperative morbidity were not different among our study groups. Three patients died in the TEA group, three in the H, and four in the NLA groups. Diminution of the stress response to surgery by afferent sensory blockade and decreased adrenergic tone with epidural anesthesia has been postulated as having beneficial effects on postoperative morbidity and mortality (42), but to date no conclusive data have been reported (14,15). Yeager et al. (3) recently observed a significantly lower incidence of cardiovascular complications, including congestive heart failure and a reduced overall complication rate in their TEA patients. While the authors attributed the improved outcome to some aspect of epidural anesthesia, their study had methodological problems that evoked much criticism (43–47). Although we found significantly smaller cortisol levels in TEA patients compared to group H intraoperatively (48), postoperative nitrogen balance and the course of several rapid turnover proteins that were monitored up to the fifth postoperative day were not statistically different among the three groups (49).

The question of the relative contribution of anesthesia to operative mortality has recently been studied by logistic regression analysis (50). The data were from an anesthesia follow-up program of patients attended by the anesthesiologists at one Canadian hospital over a 10-year period. Seven-day postoperative mortality was much more strongly predicted by

patient and surgical risk factors (e.g., age, physical status) than it was by factors relating to the anesthesia (e.g., type and duration of anesthesia, experience of anesthesiologist). Interestingly, they found a decreased mortality risk for spinal anesthesia techniques, and an increased mortality for narcotic techniques, in comparison to inhalational techniques. The authors did, however, advise caution in interpretation of the comparisons between anesthetics since the choice of drugs was not a controlled variable.

In summary, the data of this study do not support the hypothesis that thoracic epidural anesthesia is associated with beneficial effects on systemic hemodynamics and the total body O_2 supply-demand ratio. Oxygen consumption was not reduced with TEA compared to general anesthesia. Due to smaller CI, the O_2 supply-demand ratio was reduced with TEA by 10–30%. We conclude that TEA in combination with general anesthesia has no demonstrable advantages for cardiac risk patients.

References

1. Ottensen S. The influence of thoracic epidural analgesia on the circulation at rest and during physical exercise in man. Acta Anaesthesiol Scand 1978;22:537–47.

2. Reiz S, Balfors E, Sorensen BM, Haggmark S, Nyhman H. Coronary hemodynamic effects of general anaesthesia and surgery—modification by epidural analgesia in patients with ischemic heart disease. Reg Anesth 1982;7(Suppl.):S8–S18.

3. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high risk surgical patients. Anesthesiology 1987;66:728–36.

4. Heusch G, Deussen A. The effect of cardiac sympathetic nerve stimulation on perfusion of stenotic coronary arteries in the dog. Circ Res 1983;53:8–15.

5. Reiz S, Nath S, Ponten E, Friedman A, Backlund U, Olsson B, Rais O. Effects of thoracic epidural block and the beta-1-adrenoreceptor agonist prenalterol on the cardiovascular response to infrarenal cross-clamping in man. Acta Anaesthesiol Scand 1979;23:395–403.

6. Otton PE, Wilson EJ. The cardio-circulatory effects of upper thoracic epidural analgesia. Can Anaesth Soc J 1966;13:541–9.

7. Bromage PR. Vascular hypotension in 105 cases of epidural analgesia. Anaesthesia 1951;6:26–9.

8. Bonica JJ, Kennedy WF, Gerbershagen HU. Circulatory effects of peridural block. III. Effects of acute blood loss. Anesthesiology 1972;36:514–8.

9. Bromage PR. Physiology and pharmacology of epidural analgesia. Anesthesiology 1967;28:582–622.

10. Seeling W, Ahnefeld FW, Hamann H, Heinrich H, Hutschenreiter S, Rosenberg G, Spilker D. Aortofemoraler Bifurkationsbypass. Der Einfluss des Narkoseverfahrens (NLA, thorakale Katheterperiduralanaesthesie) auf Kreislauf, Atmung und

11. Bunt TJ, Manchzuk M, Varley K. Continuous epidural anesthesia for aortic surgery. Thoughts on peer review and safety. Surgery 1987;101:706–16.

12. Jansky L. Body organ thermogenesis of the rat during exposure to cold and at maximal metabolic rates. Fed Proc 1966; 25:1297–302.

13. Renck H. The elderly patient after anaesthesia and surgery. Acta Anaesthesiol Scand 1969;34(Suppl.):1–136.

14. Kehlet H. Influence of regional anesthesia on postoperative morbidity. Ann Chir Gynecol 1984;73:171–6.

15. Hjortso O, Neumann P, Frosig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. Acta Anaesthesiol Scand 1985; 29:730–6.

16. Noll F. L-(+)-Lactate. Bestimmung mit LDH, GPT and NAD. In: Bergmeyer HU, ed. Methoden der enzymatischen Analyse. 3rd ed. Weinheim: Verlag Chemie, 1974:1475–7.

17. Czok R, Lamprecht W. Pyruvat, phosphoenol pyruvat und D-glycerate-2 phosphate. In: Bergmeyer HU, ed. Methoden der enzymatischen Analyse. 3rd ed. Weinheim: Verlag Chemie, 1974:1431–93.

18. Huckabee WE. Relationship of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of pyruvate or glucose and of hyperventilation. J Clin Invest 1958;37:244–54.

19. Kaplan JA. Hemodynamic monitoring in Cardiac Anesthesia. 2nd ed. Orlando: Grune & Straton. 1987:179–225.

20. Gantz A. Experiments with three or more groups when each group contains different individuals: the Kruskal-Wallis statistic. In: Biostatistics, New York: McGraw Hill, 1987:310–2.

21. Severinghaus JW, Cullen SC. Depression of myocardium and body oxygen consumption with fluothane. Anesthesiology 1958;19:165–77.

22. Theye RA, Michenfelder JD. Whole-body and organ $\dot{V}O_2$ changes with enflurane, isoflurane and halothane. Br J Anaesth 1975;47:813–7.

23. Brismar B, Bergenwald L, Cronestrand R, Jorfeldt L, Juhlin-Dannfelt A. The cardio-vascular effects of neuroleptanalgesia. Acta Anaesthesiol Scand 1977;21:100–8.

24. Seeling W, Ahnefeld FW, Grunert A, Heinrich H, Lotz P, Rosenberg G, Wieser E. Aortofemoraler Bifurkationsbypass. Der Einfluss des Anaesthesieverfahrens (NLA, thorakale Katheterperiduralanaesthesie) auf Kreislauf, Atmung und Stoffwechsel. Anaesthesist 1986;35:80–92.

25. Skovsted P, Price ML, Price HL. The effects of halothane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 1969;31:507–14.

26. Stoelting RK, Eger EJ II. Effect of ventilation and solubility on recovery from anesthesia: an in vivo and analog analysis before and after equilibrium. Anesthesiology 1969;30:290–6.

27. Chapler CK, Cain SM. Blood flow and O_2 uptake in dog hindlimb with anemia, norepinephrine, and propranolol. J Appl Physiol 1981;51(3):565–70.

28. Bromage PR. Epidural analgesia. Philadelphia: Saunders, 1978.

29. Shepherd AP, Granger HJ, Smith EE, Guyton AC. Local control of tissue oxygen delivery and its contribution to regulation of cardiac output. Am J Physiol 1973;225:747–55.

30. Gersh BJ, Prys-Roberts C, Reuben SR, Schultz DL. The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance II: Aortic input impedance, and the distribution of energy during ventricular ejection. Br J Anaesth 1972;44:767–75.

31. Baron JF, Decaux-Jacolot A, Edouard A, Berdeaux A, Samii K. Influence of venous return on baroreflex control of heart rate

during lumbar epidural anesthesia in humans. Anesthesiology 1986;64:188–93.

32. Eger EG, Smith NT, Stoelting RK, Cullen DJ, Kadis LB, Whitcher CE. Cardiovascular effects of halothane in man. Anesthesiology 1970;32:396–401.

33. Derbyshire DR, Smith G: Sympathoadrenal responses to anaesthesia and surgery. Br J Anaesth 1984;56:725–36.

34. Chidsey CA, Braunwald E, Morrow AG. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. Am J Med 39:442–51.

35. Gaffney TE, Braunwald E. Importance of the adrenergic nervous system in the support of circulatory function in patients with congestive heart failure. Am J Med 1969;34:320–4.

36. Mason DT. The autonomic nervous system and regulation of cardiovascular performance. Anesthesiology 1968;29:670–80.

37. Hickham JB, Cargill WH. Effects of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J Clin Invest 1948;27:10–8.

38. Schlichtig R, Cowden VL, Chaitman BR. Tolerance of unusually low mixed venous oxygen saturations adaptations in the chronic low cardiac output syndrome. Am J Med 1986;80:813–8.

39. Glick G, Plauth WH, Braunwald E. Role of the autonomic nervous system in the circulatory response to acutely induced anemia in unanesthetized dogs. J Clin Invest 1964;43:2112–24.

40. Johansen SH, Laver MB. Cardiovascular effects of severe anemic hypoxia. Acta Anaesthesiol Scand 1966;24(Suppl.):63–73.

41. Heistad DD, Abboud FM. Circulatory adjustments to hypoxia. Circulation 1980;61:463–70.

42. Kehlet H. Stress free anaesthesia and surgery. Acta Anaesthesiol Scand 1979;23:503–8.

43. Kehlet H. Epidural anesthesia and analgesia in high risk surgical patients I (letter). Anesthesiology 1987;67:1022–3.

44. Frumin MJ. Epidural anesthesia and analgesia in high risk surgical patients II (letter). Anesthesiology 1987;67:1023–4.

45. Jenkins JG. Epidural anesthesia and analgesia in high risk surgical patients III (letter). Anesthesiology 1987;67:1024–5.

46. Day J. Epidural anesthesia and analgesia in high risk surgical patients IV (letter). Anesthesiology 1987;67:1025.

47. Clark JL. Epidural anesthesia and analgesia in high risk surgical patients V (letter). Anesthesiology 1987;67:1025–6.

48. Stelzner J, Reinhart K, Foehring M, Henneberg M, Schaefer M, Fitzner R. Influence of thoracic epidural analgesia on the cortisol response to major transabdominal surgery. Reg Anesth 1988;11:16–20.

49. Foehring U, Reinhart K, Schaefer M, Dennhardt R. Epidural analgesia does not modify metabolic response to major surgery (abstr). Crit Care Med 1986;14:329.

50. Cohen MM, Duncan PG and Tate RB. Does anesthesia contribute to operative mortality? JAMA 1988;260:2859–63.

Solubility of I-653, Sevoflurane, Isoflurane, and Halothane in Human Tissues

Nobuhiko Yasuda, MD, Alexander G. Targ, MD, and Edmond I. Eger II, MD

YASUDA N, TARG AG, EGER EI II. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989;69:370-3.

Tissue/blood partition coefficients of anesthetics are important indicators of the rate of tissue wash-in and wash-out, and wash-in and wash-out are determinants of the rates of induction of and recovery from anesthesia. In the present study of human tissues, we found that the tissue/blood partition coefficients (for brain, heart, liver, kidney, muscle, and fat) for the new anesthetic I-653 were smaller than those for isoflurane, sevoflurane, and halothane (anesthetics listed in order of increasing tissue/blood partition coefficients). For example, the respective brain/blood partition coefficients were 1.29 ± 0.05 (mean ± SD); 1.57 ± 0.10; 1.70 ± 0.09; and 1.94 ± 0.17. This indicates that induction of and recovery from anesthesia with I-653 should be more rapid than with the other agents. The finding of a lower tissue/blood partition coefficient for I-653 parallels the previous finding of a lower blood/gas partition coefficient.

Key Words: ANESTHETICS VOLATILE—halothane, I-653, isoflurane, sevoflurane. PHYSICS, SOLUBILITY—volatile anesthetics.

Recovery from anesthesia with the new inhaled anesthetic, I-653, is more rapid than recovery from other potent inhaled agents (1). Although a major part of the rapidity of recovery is due to the low blood/gas partition coefficient (0.42) (2), low tissue/blood partition coefficients (especially a low brain/blood partition coefficient) may also be factors. A knowledge of tissue solubility also is required for simulation of anesthetic pharmacokinetics. Accordingly, we have simultaneously determined the tissue/gas partition coefficients of I-653, sevoflurane, isoflurane, and halothane in human brain, heart, liver, kidney, muscle, and fat, and calculated the respective tissue/blood partition coefficients.

Materials and Methods

We determined tissue/gas partition coefficients with a modification of a method used previously (3). Specimens of adult human brain, heart, liver, kidney, muscle, and fat were obtained at autopsy within 48 hr of death. Specimens were obtained from 14 patients, but not all tissues were obtained from all patients (e.g., permission might not have been given to examine the brain, tumor may have invaded the liver). We excluded from our study, specimens collected from patients dying from infectious diseases or from diseases that might alter tissue components (e.g., congestive heart failure). Immediately after collection, tissues were prepared as follows. Arachnoid and pial membranes and vascular structures were stripped from brain (frontal lobe; roughly equal proportions of grey and white matter). We discarded pericardial membrane and endocardial lining from heart. For liver and kidney we removed the capsule, vessels, and ducts. We eliminated fascial structures and all visible fat from (psoas) muscle. We removed the vascular structures from (perirenal) fat. Each tissue was sliced into small cubes. An aliquot of tissues thus prepared was added to a precisely known volume of saline, and the total volume of tissue was measured by volume displacement. The tissue:saline volume ratio was in the range of 1:1-2, depending on the tissue. This mixture was homogenized using a Kinematica CH-6010 Kriens-Lu homogenizer at room temperature (about 22-24°C) after addition of a trace of antifoaming agent. The homogenate was frozen at −70°C until determination of the partition coefficient.

Table 1. Human Tissue/Gas Partition Coefficients

Tissue	n	Patient Age (yr)	Tissue/Gas Partition Coefficient			
			I-653	Sevoflurane	Isoflurane	Halothane
Brain	6	65.7 ± 20.7	0.54 ± 0.02	1.15 ± 0.07	2.09 ± 0.10	4.79 ± 0.38
Heart	8	58.3 ± 20.9	0.54 ± 0.07	1.21 ± 0.13	2.18 ± 0.28	4.60 ± 0.77
Liver	10	64.7 ± 18.1	0.55 ± 0.06	1.25 ± 0.15	2.34 ± 0.30	5.13 ± 0.67
Kidney	10	67.4 ± 14.2	0.40 ± 0.05	0.78 ± 0.12	1.39 ± 0.24	2.85 ± 0.54
Muscle	9	63.7 ± 18.0	0.94 ± 0.35	2.38 ± 1.03	4.40 ± 1.97	9.49 ± 4.55
Fat	9	60.3 ± 17.7	12.0 ± 2.0	34.0 ± 6.0	64.2 ± 12.3	136 ± 33

Values are shown as mean ± SD.

Each homogenate was thawed in a waterbath at 37°C. The homogenate was shaken vigorously, and approximately 10 mL of the homogenate was introduced into a 30 mL glass syringe capped with a three-way stopcock. The plunger of the syringe was lubricated with a trace of Teflon grease. Fifteen to 20 mL of a mixture of 1.0%–1.1% I-653, 0.4%–0.6% sevoflurane, 0.4%–0.6% isoflurane, and 0.5% halothane in 20%–30% oxygen (balance nitrogen) was added. The syringe was shaken vigorously and placed on a rotator in a waterbath at 37°C for 1.5–2 hr. Each syringe was shaken vigorously every 20 min during this time. Previous studies have shown that equilibrium is reached in this period of time (4). After the 1.5–2 hr of equilibration, the concentrations of the anesthetics in the gas phase were analyzed.

An aliquot of the homogenate (5.05 mL) was injected into an evacuated flask of known volume (about 575 mL). The flask had a Teflon stopper pierced with two needles surmounted by one-way stopcocks, one for introduction of the homogenate and the other for gas sampling. The stopper was coated at its upper portion with a small amount of Teflon grease to insure sealing. The flask was shaken at 15–20 min intervals. During the intervening time the flask resided in a waterbath maintained at 37°C. The pressure within the flask was equilibrated with ambient pressure by briefly opening the stopcock after about 1 hr. At this time, 20 mL of room air was injected into the flask.

The gas phase in the flask was sampled after 1.5 hr of tonometry. Using a 50 mL glass syringe attached to the sampling stopcock, the gas in the flask was barbotaged by injecting and withdrawing 20 mL 20 times. A sample was taken after the 20th injection.

All samples were analyzed for anesthetic concentrations by gas chromatography. We used a Gow Mac Model 750 gas chromatograph equipped with a 30-m-long, fused silica open tubular capillary column (0.53 mm internal diameter) coated with a 5-μ-thick layer of methylsilicone oil (J & W Scientific DB-1) maintained at 40°C. A nitrogen carrier stream of 12–14 mL/min was directed through the column with

Table 2. Human Tissue/Blood Partition Coefficients

Tissue	Tissue/Blood Partition Coefficient			
	I-653	Sevoflurane	Isoflurane	Halothane
Brain	1.29 ± 0.05	1.70 ± 0.09	1.57 ± 0.10	1.94 ± 0.17
Heart	1.29 ± 0.17	1.78 ± 0.20	1.61 ± 0.24	1.84 ± 0.33
Liver	1.31 ± 0.14	1.85 ± 0.22	1.75 ± 0.24	2.07 ± 0.29
Kidney	0.94 ± 0.13	1.15 ± 0.18	1.05 ± 0.19	1.16 ± 0.22
Muscle	2.02 ± 0.58	3.13 ± 1.07	2.92 ± 1.06	3.38 ± 1.36
Fat	27.2 ± 3.0	47.5 ± 6.1	44.9 ± 5.5	51.1 ± 9.5

Values are shown as mean ± SD.

a "make-up" flow of nitrogen of 40 mL/min delivered to the detector. A flame ionization detector at 170°C was supplied by hydrogen at 40–50 mL/min and by air at 200–240 mL/min. Samples were injected with a 0.05 or 0.1 mL gas sample loop. The chromatograph was calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic into a flask of known volume.

All measurements for each tissue were run in duplicate. We discarded values which deviated from the mean of the duplicate by more than 10%. The duplicate values for each tissue from a given patient were averaged.

The homogenate/gas partition coefficient ($\lambda_{h/g}$) was calculated as:

$$\lambda_{h/g} = \frac{C_f}{C_s - C_f} \cdot \frac{V_f}{V_s}$$

where C_s and C_f are the anesthetic concentrations in the gas phase of the syringe and flask, and V_s and V_f are the volumes of the homogenate aliquot introduced into the flask and of the flask, respectively. The tissue/gas partition coefficients ($\lambda_{t/g}$) were calculated by mass balance, using the equation:

$$\lambda_{t/g} = \lambda_{h/g} + \frac{V_{sal}}{V_{tis}} \cdot (\lambda_{h/g} - \lambda_{sal})$$

where λ_{sal} is the saline/gas partition coefficient, V_{tis} and V_{sal} are the volume of tissue and saline in the homogenate, respectively.

Tissue/gas partition coefficients for the four anesthetics were converted to tissue/blood partition coef-
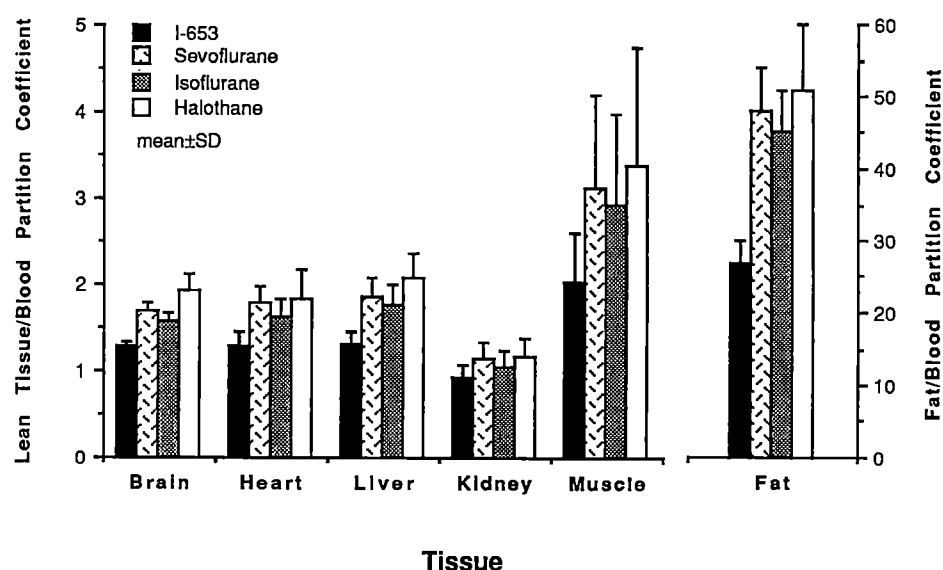
Figure 1. The tissue/blood partition coefficients of I-653 for each tissue were smaller than those of isoflurane, sevoflurane and halothane ($P < 0.01$) (values are shown as mean ± SD).
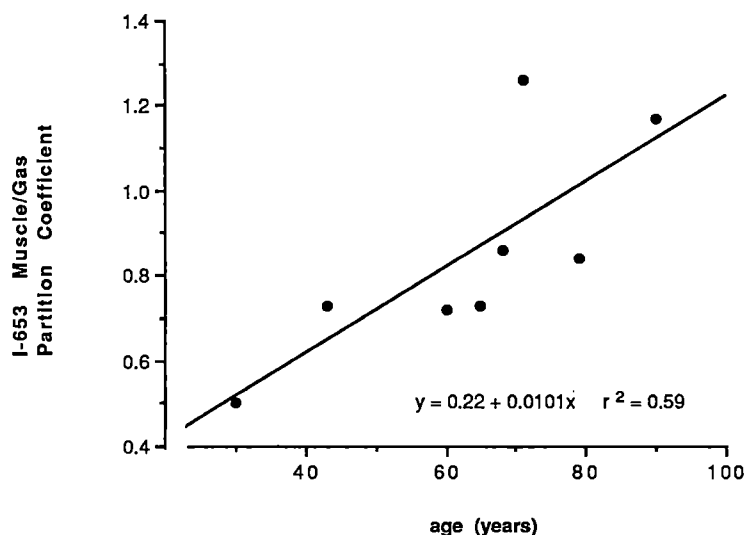
Figure 2. I-653 muscle/gas partition coefficient increases, and correlates significantly ($P < 0.05$) with an increase in age.

ficients ($\lambda_{t/b}$) by dividing the tissue/gas partition coefficient by the published values for the blood/gas coefficients adjusted for age (2,4,5). The tissue/gas and tissue/blood partition coefficients were compared using analysis of variance with repeated measures and Student-Newman-Keuls method of multiple comparisons. A P value of less than 0.05 was considered statistically significant. Using regression, we examined whether the tissue/gas or tissue/blood partition coefficients for each tissue and anesthetic correlated with patient age.

Results

The average age of the patients was 65.8 ± 14.4 years of age (mean ± standard deviation). Three out of 55 cases of measurements of tissue/gas partition coeffi-

cients were discarded because the duplicates deviated more than 10% from their mean. The order of tissue/gas partition coefficients was halothane > isoflurane > sevoflurane > I-653 (Table 1). All of the tissue/gas partition coefficients were significantly different ($P < 0.01$) across agents, except that the muscle/gas partition coefficients for I-653 and sevoflurane did not differ. The order of the tissue/blood partition coefficients was halothane > sevoflurane > isoflurane > I-653. As with the tissue/gas partition coefficients, most of the tissue/blood partition coefficients were significantly different across agents ($P < 0.05-0.01$) (Table 2; Figure 1). However, heart/blood, kidney/blood, and muscle/blood partition coefficients were not different for sevoflurane and halothane, and muscle/blood and fat/blood partition coefficients were not different for isoflurane and sevoflurane.

Correlation between age and tissue/gas or tissue/blood partition coefficients could not be shown except for muscle/gas and muscle/blood partition coefficients. Muscle/gas and muscle/blood partition coefficients increased with increasing age (Figure 2).

Discussion

Tissue/gas partition coefficients previously reported by several investigators for halothane and isoflurane are equal to or greater than those we found. Larson et al. found values for halothane that were close to those that we found for brain, liver, kidney, muscle, and fat (no values were reported for heart) (6). Lerman et al. found values for isoflurane and halothane that were similar to those reported in the present study (3). Given that Larson et al. and Lerman et al. used the same technique and worked in our laboratory, the similarity of our findings to theirs is not surprising. However, the values for isoflurane found by Lowe were 50%–75% greater than ours (7). The values for sevoflurane, isoflurane, and halothane found by Fiserova-Bergerova et al. were similar to ours for brain and fat (excluding the fat/gas partition coefficient for halothane which was 65% greater than ours), 30%–80% greater for liver, 115%–150% greater for kidney, and 10%–30% less than our values for muscle (8). Difference in technique may explain our generally lower values, but no specific explanations can be given. In general, the tissue/gas partition coefficients obtained by Fiserova-Bergerova et al. had a larger variability than our tissue/gas partition coefficients. They used a smaller total volume of tissue and saline and a greater proportion of saline, and performed repeated samplings from the incubation tubes. (More samplings increase the loss of anesthetic from the incubation tubes. The result would be an increased estimate of the amount of anesthetic dissolved into the homogenate and thus an increased partition coefficient.) They also used weight instead of volume of the tissues. Such differences in methods and/or differences in sample population may cause the discrepancies between our results.

We found that the tissue/gas and tissue/blood partition coefficients for I-653 are lower than the respective partition coefficients for other potent inhaled anesthetics (Tables 1 and 2; Figure 1). The solubilities in tissues lie between those for the potent agents and those associated with nitrous oxide (9). Thus the rapid recovery seen with I-653 is due to both its low solubility in blood and its low solubility in tissues. The lower tissue solubility mediates a more rapid recovery by two mechanisms. First, the brain time constant will be shorter. Second, the elimination of I-653 from the body will be more rapid.

Although Lerman et al. (3) have shown several correlations between age and tissue solubility, the only correlation that we found was for muscle (Figure 2). Our results are consistent with those of Lerman et al., both showing an increase in solubility with increasing age. This increase probably results from the progressive increase in fat deposits in muscle with aging. The absence of a correlation with age for other tissues probably resulted from a lower number of determinations in our study.

References

1. Eger EI II, Johnson BH. Rate of awakening from I-653, halothane, isoflurane, and sevoflurane in rats: A test of the effect of anesthetic concentration and duration. Anesth Analg 1987;66:977–82.

2. Eger EI II. Partition coefficients for I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.

3. Lerman J, Schmitt-Bantel BI, Gregory GA, Willis MM, Eger EI II. Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology 1986;65:307–11.

4. Eger RR, Eger EI II. Effect of temperature and age on the solubility of enflurane, halothane, isoflurane, and methoxyflurane in human blood. Anesth Analg 1985;64:640–2.

5. Strum DP, Eger EI II. Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesth Analg 1987;66:654–6.

6. Larson CP, Eger EI II, Severinghaus JW. The solubility of halothane in blood and tissue homogenates. Anesthesiology 1962;23:349–55.

7. Lowe HJ. Partition coefficients for enflurane and isoflurane. Isoflurane New Drug Application 1975:2947.

8. Fiserova-Bergerova V, Tichy M, Di Carlo FJ. Effects of biosolubility on pulmonary uptake and disposition of gases and vapors of lipophilic chemicals. Drug Meta Rev 1984;15:1033–70.

9. Eger EI II. Pharmacokinetics. In: Eger EI II ed. Nitrous Oxide/N₂O. New York: Elsevier, 1985:81–103.

The Effects of Airway Impedance on Work of Breathing during Halothane Anesthesia

Teresa A. Slee, MD, Samuel R. Sharar, MD, Edward G. Pavlin, MD, and
Pamela E. MacIntyre, MD

SLEE TA, SHARAR SR, PAVLIN EG, MACINTYRE PE.
The effects of airway impedance on work of breathing
during halothane anesthesia. Anesth Analg 1989;69:374-8.

Humidifiers and small diameter endotracheal tubes placed
in the airway circuit increase the impedance to breathing.
The effect of such impedances on the work of breathing and
respiratory patterns was studied in eight healthy adult
patients (60–80 kg) anesthetized with 1 and 2 MAC
halothane in oxygen. A Cascade Humidifier and Portex
Humid-Vent (dry and water saturated) were evaluated
while patients breathed through an 8.0-mm endotracheal
tube. A 6.0-mm endotracheal tube was also assessed with-
out the humidifiers. At 1 MAC the Cascade Humidifier and

the wet Humid-Vent when used with the 8.0-mm tube
increased the work of breathing to 86.8 ml and 76.8 ml,
77% and 70% above baseline levels of 48.1 ml, whereas the
6.0-mm tube without the humidifiers increased work 89%
to 78.9 ml. Tidal volume and respiratory frequency were
unchanged throughout the study, although inspiratory time
was prolonged. Lightly to moderately anesthetized healthy
adult patients are able to maintain minute ventilation
despite the impedance associated with commonly used
humidifiers by significantly increasing work of breathing.

Key Words: VENTILATION, WORK OF
BREATHING—impedance.
EQUIPMENT, HUMIDIFIERS.

Humidification of inspired gases, a common adjunct to general anesthesia, is important in the maintenance of core temperature, normal ciliary activity in the trachea (1), and lung mechanics (2,3). However, the equipment used for humidification adds impedance to the breathing circuit. The awake individual can maintain minute ventilation in response to an increased inspiratory impedance (4). However, some reflexes presumed to be involved in maintaining adequate ventilation are depressed in a dose related way during general anesthesia, for example hypoxic ventilatory drive (5) and ventilatory response to CO_2 (6). The primary purpose of this study was to determine what effects the impedance associated with commonly used humidifiers and small diameter endotracheal tubes has on the work of breathing, respiratory patterns, and minute ventilation in adults anesthetized with 1 and 2 MAC halothane. Secondly, we, like others (7,8,9), used work of breathing to

assess the impedance of airway equipment during alternating flow conditions.

Airway equipment resistance is usually evaluated under continuous gas flow conditions. However, this method does not simulate clinical conditions and may underestimate the total impedance. Impedance, which defines the relationship between pressure and flow, has components of both resistance and capacitance. Measurements obtained during continuous flow conditions only reflect the effect of resistance. Using various airway equipment, we measured resistance during continuous flow as well as effective impedance during phasic flow. Effective impedance describes the work required to move a volume of respired gas through the breathing circuit (7) during alternating flow.

Methods

Eight ASA I or II adult patients, weighing 60–80 kg, scheduled for elective surgery were enrolled in the study. The study protocol had been approved by the University of Washington Human Subjects Committee. Informed consent was obtained from all subjects before commencing the study.

Preoperative medications were not ordered. Studies were performed before surgical stimulation. After standard monitors were applied, anesthesia was induced by breathing halothane and oxygen. Under deep halothane anesthesia, 4% lidocaine spray was applied to the larynx before intubating the patient's trachea with an 8.0-mm ID endotracheal tube. Anesthesia was maintained solely with halothane and oxygen; the patients breathed without assistance during the entire experiment.

End-tidal (PetHAL) concentrations were continuously measured with use of a Perkins Elmer 1100 Medical Gas Analyzer. Intrapleural pressure was determined from an esophageal balloon. Airway pressure and inspiratory and expiratory flow rates were measured from a Fleisch pneumotachograph placed at the distal end of the endotracheal tube. Pressure and flow signals were processed by an analog computer (Buxco Electronics Inc., Pulmonary Analyzer Model 6) to determine tidal volume (Vt), respiratory rate (f), minute ventilation ($\dot{V}E$), inspiratory time (Ti), and work of breathing. Work of breathing (W), the energy expended to move a volume of gas during a breath, is the product of the Vt multiplied by the airway pressure (P) integrated over a single respiratory cycle;

$$OW = \int PdVt$$

Therefore, the raw data was expressed as cm H_2O mL, which was converted to mJ.

Baseline measurements were made with the patient's trachea intubated with an 8.0-mm ID endotracheal tube at both 0.8% and 1.6% halothane anesthesia. Patients were maintained at each anesthetic level for at least 15 min before measurements. After baseline measurements, one of the humidifiers was added to the circuit. After about 5 min when subjects had reached a new steady state of intrapleural pressure, measurements were repeated, the humidifier removed, and a different humidifier added and studied. The humidifier was removed and the 8.0 endotracheal tube was replaced with a 6.0 tube, and the variables were measured at 1 and 2 MAC levels. At the conclusion of the experiment, the patient was reintubated with the 8.0 endotracheal tube and taken to the operating room where the surgery commenced. The humidifiers tested were the Bennett Cascade II Column Mount humidifier (Model No 9364), and a Portex disposable Humid-Vent (artificial nose) both dry and saturated with water vapor.

The impedance of each piece of equipment was assessed by two methods. First, the resistance of each humidifier was measured with use of continuous gas

flow conditions. The pneumotachograph was positioned immediately proximal to the humidifier or endotracheal tube being tested. The other end was unobstructed. The Cascade Humidifier was tested with its connecting tubing in place as this is how it is used under clinical conditions. A flow of 35–40 L/min of oxygen was maintained as the pressure drop across each piece of equipment was measured. Resistance was calculated by dividing the pressure difference by the flow. Secondly, the mean work of breathing associated with each piece of equipment measured during the experiment was normalized to $\dot{V}E$ as an index of effective impedance [7]. Other investigators [7,8,9] have used measurements of work of breathing to assess the impedances of various types of airway equipment. However, unlike them, we choose to use human subjects rather than a mechanical pump to measure work of breathing. A mechanical pump has a set I:E ratio, whereas humans may alter their I:E ratio in response to an impedance. Work of breathing would be affected because flow would change. Therefore, the work and consequently the effective impedance associated with a piece of equipment might be different from that calculated under laboratory conditions because of human adaption.

The data were analyzed for statistical significance with use of the analysis of variance for repeated measurements and Dunnet's test. Statistical significance was assumed if the P valve was <0.05.

Results

Data on work of breathing, $\dot{V}E$, Vt, Ti, and f are summarized on Table 1. There was no significant change in f at either the 1 or 2 MAC halothane levels with any of the impedances. At 1 MAC halothane, the impedances had no significant effect on Vt or $\dot{V}E$. Although Vt and $\dot{V}E$ decreased with increased anesthetic depth, again the addition of the impedances produced no significant additional changes. AT 1 MAC halothane, the work of breathing increased with all the impedances. The increase in work achieved statistical significance when the water saturated Humid-Vent, the 6.0 endotracheal tube, and the Cascade Humidifier were tested.

At 2 MAC, there was an expected decrease in Vt that resulted in a 20% decrease in work of breathing. Work of breathing tended to increase when the various impedances were added, but statistical significance was achieved only with the 6.0 endotracheal tube. Overall, Ti was prolonged when an impedance was added. The increase in Ti during testing of the Cascade Humidifier at 1 and 2 MAC was significant.

Table 1. The Responses of Impedances Measured at 1 and 2 MAC Halothane Anesthesia

	MAC	Frequency (breath/min) ($\pm$SE)	Tidal Volume (mL) ($\pm$SE)	Minute Ventilation (L/min) ($\pm$SE)	Work Per Breath (mJ) ($\pm$SE)	Inspiratory Time (sec) ($\pm$SE)
Baseline (8.0 OETT)	1	29.7 ± 1.6	273.1 ± 17.6	8.01 ± 0.51	48.1 ± 7.7	0.77 ± 0.07
	2	30.8 ± 1.4	199.1 ± 23.6	6.07 ± 0.39	35.5 ± 8.0	0.71 ± 0.08
Dry humid-vent (8.0 OETT)	1	28.0 ± 1.5	272.6 ± 15.2	7.58 ± 0.49	50.9 ± 9.7	0.82 ± 0.08
	2	29.8 ± 1.3	205.1 ± 27.7	6.03 ± 0.50	38.2 ± 7.9	0.73 ± 0.07
Sat humid-v (8.0 OETT)	1	26.6 ± 1.2	258.6 ± 8.3	6.90 ± 0.38	76.8 ± 10.7*	0.87 ± 0.09
	2	31.6 ± 1.8	205.4 ± 31.2	6.07 ± 0.53	40.1 ± 8.4	0.76 ± 0.09
Cascade (8.0 OETT)	1	27.0 ± 1.3	310.5 ± 12.3	7.36 ± 0.28	86.8 ± 12.7*	0.89 ± 0.09*
	2	30.1 ± 2.3	274.6 ± 27.4	5.85 ± 0.31	57.2 ± 10.5	0.77 ± 0.10*
6.0 OETT (Alone)	1	27.4 ± 1.5	310.5 ± 19.9	7.41 ± 0.31	78.9 ± 15.8**	0.81 ± 0.10
	2	30.4 ± 2.6	208 ± 25.1	6.17 ± 0.36	57.5 ± 10.2*	0.79 ± 0.09

**$P < 0.01$; *$P < 0.05$.
Abbreviation: OETT, Oral endotracheal tube.

Table 2. Impedance Characteristics of Devices Tested

Apparatus	Continuous Flow Resistance (cm H_2O/L/sec)	Phasic Flow Effective Impedance, Work of Breathing/$\dot{V}_E$ (mJ/L/min)
Dry Humid-Vent	5.2	6.52
Sat. Humid-Vent	9.5	8.87
Cascade	9.4	10.78
6.0 Endotracheal	16	9.99

Resistance and normalized work of breathing measurements are shown on Table 2. Resistance was greatest across the 6.0 endotracheal tube followed by the saturated Humid-Vent and the Cascade Humidifier. Normalized work of breathing was greatest across the Cascade Humidifier, followed by the 6.0 endotracheal tube, then the saturated Humid-Vent.

Discussion

Nunn and Ezi-Ashi (10) studied the response of human subjects to threshold resistors (inspiratory and expiratory) as well as tubular resistors using different anesthetic techniques and different depths of anesthesia. Threshold resistors allow gas flow only when the threshold pressure is equaled or exceeded, at which point increases in flow are associated with only small increases in pressure (11). They found that respiratory compensation in response to threshold resistors, when it occurred, was complete by 90 sec. Although there was considerable variation, there appeared to be a correlation in their study between the ability to maintain $\dot{V}_E$ and the magnitude of impedance imposed. The range of threshold resistances was between 2 and 17 cm H_2O. Nunn and Ezi-Ashi also demonstrated that ventilatory compen-

sation was achieved by increasing negative pressure with the first obstructed breath.

Moote et al. (12) studied in humans three different sizes of elastic and resistive inspiratory loads. All their measurements were made at 1 MAC halothane. They found that after 2 min of equilibration $\dot{V}_E$ had returned to baseline levels with both small and medium inspiratory loads. $\dot{V}_E$ decreased with the large inspiratory loads, but f was unchanged regardless of the impedance. They also found that the ratio between dead space and tidal volume (V_D/V_T) was unaffected by the inspiratory loading.

We have evaluated the response of patients anesthetized with halothane to several clinically relevant ventilatory impedances. The Cascade Humidifier has characteristics similar to those of a mixed capacitor and threshold resistor and acts on the inspiratory side of the circuit. A capacitor is an impedance that effects the pressure flow relationship during alternating flow by storing and then releasing energy. The Humid-Vent is primarily a resistive impedance that affects both inspiratory and expiratory flows. The 6.0 endotracheal tube is a tubular resistor. Our study differs from that of Nunn and Ezi-Ashi (10) in that we used a uniform anesthetic technique, and measurements were made before surgical stimulation. Our protocol was somewhat similar to that of Moote et al. (12) except that we studied both 1 and 2 MAC halothane. Furthermore, we studied the effects of clinically used equipment and measured the work of breathing.

As with other studies (4,10,12–15), we observed that the f was unchanged from baseline in response to an increase in inspiratory impedance. We also found no changes in V_T or $\dot{V}_E$ regardless of the impedance used at 1 MAC halothane. At deeper levels of halothane anesthesia f, V_T and $\dot{V}_E$ were

maintained in the face of the impedances we tested. Other reflexes, including ventilatory responses to CO_2 and hypoxia are depressed in a dose related fashion during inhalational anesthesia. We found that the mechanism that allows patients to maintain their $\dot{V}E$ against a respiratory impedance appeared to still be intact even at this deeper anesthetic level.

Work of breathing decreased with 2 MAC halothane. The decrease in work was related to the decrease in VT observed at deeper levels of anesthesia. It is unlikely that the decrease in work of breathing was caused by changes of airway resistance because there was little difference in the baseline measurements of work of breathing normalized to minute ventilation at 1 MAC (6.0 mJ/L/min) compared with 2 MAC (5.84 mJ/L/min). When an impedance was added to the airway, there was still an increase in the work of breathing. This increase was significant, especially at the 1 MAC halothane level. However, this represents a small increase in the total oxygen consumption. The energy expended during ventilation under normal circumstances in unanesthetized healthy patients is small in the order of 3–4 mL of oxygen/min during quiet breathing (16).

Any increases in work of ventilation that we observed were associated with the increase in transpleural pressure needed to maintain a constant VT in the presence of an impedance. This is consistent with the findings of Nunn and Ezi-Ashi (10). Furthermore, we found that imposition of an impedance was associated with an increase in Ti that occurred at both anesthetic levels. This finding is consistent with that of Whitelaw et al. (15) who studied the response of Ti in humans anesthetized with methoxyflurane to the addition of large (40.4 cm $H_2O/1^{s-1}$) inspiratory loads. They found that "Ti with the resistor was longer than Ti without the resistor even at the same tidal volume."

The usual method of assessing the impedance characteristic of airway equipment consists of measuring the decrease in pressure across the equipment at a known gas flow. However, flow during respiration is phasic and bi-directional. Therefore, measurements made with continuous gas flows underestimate the impedance of equipment that has capacitance characteristics. One proposed method for measuring impedance is to assess the added work imposed by a particular airway circuit or piece of equipment. Bolder et al. (8) and Kay et al. (9) measured the work of breathing associated with endotracheal tubes and anesthetic circuits respectively as a means of comparing impedance during alternating flow conditions. We, likewise, used work of breathing to estimate impedance. However, they used a

mechanical pump that was thought to be "informative . . . assuming no adaptation by the patient" (17). The patients do adapt to ventilatory impedances measured by the change in Ti. Therefore, we choose to use the work of breathing measurements obtained during patient testing. The Cascade Humidifier, unlike the other equipment tested, has capacitance characteristics, which may explain why the normalized work of breathing measurements obtained were greater than would have been expected from the resistance measurement made under continuous flow conditions.

We demonstrated that clinically used devices that offer an impedance to ventilation, e.g. humidifiers and small diameter endotracheal tubes, effect similar respiratory responses as those seen when experimental apparatus with similar resistances are studied. Additionally, we demonstrated that there is a statistically significant increase in the work of breathing associated with the use of the devices that increase ventilatory impedance as evidenced by an increase in inspiratory pressure during spontaneous respiration. Tidal volume was maintained by the associated increase in inspiratory time. Despite the increase in work of breathing, patients without respiratory impairment were able to maintain minute ventilation. This result was observed at both 1 MAC and 2 MAC levels of halothane. We conclude that normal adults without respiratory disease are able to maintain adequate minute ventilation when anesthetized with light to moderate levels of halothane in the presence of small to moderate increases in ventilatory impedance.

References

1. Chalon J, Loew DAY, Malebranche J. Effects of dry anesthetic gases on tracheobronchial ciliated epithelium. Anesthesiology 1972;37:338–43.
2. Rashad K, Wilson K, Hurt H, Graff TD, Benson DW. Effect of humidification of anesthetic gases on static compliance. Anesth Analg 1967;46:127–32.
3. Noguchi H, Takumi Y, Aochi O. A study of humidification in tracheostomized dogs. Br J Anaesth 1973;45:844–7.
4. Campbell EJ, Dickson CJ, Dinnick OP, Howell JB. The immediate effects of threshold loads on the breathing of men and dogs. Clin Sci 1961;21:309–20.
5. Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia. Anesthesiology 1982;57:151–2.
7. Wajskol A, Morris L. The dynamic measurement of effective impedance in anesthesia apparatus. Anesthesiology 1982; 57:A488.
8. Bolder PM, Healy TEJ, Bolder AR, Beatty PCW, Kay B. The extra work of breathing through adult endotracheal tubes. Anesth Analg 1986;65:853–9.
9. Kay B, Beatty PCW, Healy TEJ, Accoush MEA, Calpin M. Change in work of breathing imposed by five anaesthetic breathing systems. Br J Anaesth 1983;55:1239–46.

Isoflurane-Induced Hypotension in Orthognathic Surgery

Martin R. Lessard, MD, Claude A. Trépanier, MD, FRCPC, Jean-Pierre Baribault, MD, FRCPC,

Jacques G. Brochu, MD, FRCPC, Claude A. Brousseau, MD, FRCPC,

Jacques J. Coté, MD, FRCPC, and Pierre H. Denault, MD, FRCPC

LESSARD MR, TRÉPANIER CA, BARIBAULT J-P, BROCHU JG, BROUSSEAU CA, COTÉ JJ, DENAULT PH. Isoflurane-induced hypotension in orthognathic surgery. Anesth Analg 1989;69:379–83.

The effect of isoflurane-induced hypotension on reduction of blood loss, improvement of surgical field, and postoperative edema was investigated in 52 patients undergoing combined maxillary and mandibular osteotomies. Anesthesia was maintained with fentanyl, N_2O, O_2, and isoflurane. Deliberate hypotension was induced by increasing isoflurane inspired concentration. Blood loss in the hypotensive group (MAP 55–65 mm Hg) was significantly less than that in the control group (MAP 75–85 mm Hg): 454.0 ± 211.3 mL versus 755.3 ± 334.6 mL (P < 0.001). Fewer patients had to be transfused in the hypotensive group, 12.0% versus 44.4% (P < 0.02). The surgical field was significantly improved by the hypotensive technique, but operative time was not shortened. Subjective and objective measurements of postoperative edema failed to show any effect of deliberate hypotension. Our data suggest that isoflurane-induced hypotension effectively reduces blood loss and the number of transfusions in orthognathic surgery.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE. ANESTHETICS, VOLATILE, ISOFLURANE. BLOOD PRESSURE, HYPOTENSION. SURGERY, DENTAL.

Since deliberate hypotension was introduced into clinical practice by Griffiths and Gillies (1) several years ago, many different techniques have been proposed, but their effectiveness in reducing blood loss has been demonstrated only for a few procedures (e.g., hip surgery, spine surgery, cancer surgery) (2–5). The three proposed benefits of induced hypotension are a decrease in blood loss with a concomitant reduction in transfusions, an improved surgical field resulting in better dissection and less tissue trauma, and finally a reduction in operative time.

Although its effectiveness in orthognathic surgery is assumed by many anesthesiologists, there are no data in the literature supporting this belief. A few uncontrolled anecdotal reports proposed different hypotensive techniques (6–9), but the only controlled study we could find does not support its routine use in orthognathic surgery (10). In this prospective study, Fromme et al. (10) found that hypotension did not result in a statistically significant decrease in

blood loss or an improvement in the surgical conditions. However, their data show a trend toward a reduction in blood loss in the hypotensive groups, but the small size of their groups did not allow them to rule out a possible beneficial effect of controlled hypotension in orthognathic surgery. Moreover, the majority of their patients (62.5%) received transfusions emphasizing the need of searching for strategies to decrease transfusions and their related risks.

Another problem specific to orthognathic surgery is the postoperative edema that can be important enough to cause airway obstruction. The influence of controlled hypotension on postoperative edema in orthognathic surgery has not been studied. This study was designed to evaluate whether deliberate hypotension induced with isoflurane could significantly reduce operative blood loss, improve the surgical field, and decrease operative time in orthognathic surgery. Our second objective was to evaluate its effect on postoperative edema.

Methods

We prospectively studied 52 ASA physical status I patients free of cardiovascular, cerebrovascular, or

hematologic diseases. All patients were undergoing an orthognathic procedure involving a LeFort I maxillary osteotomy with a mandibular osteotomy. In a preliminary survey, we estimated a mean blood loss of 500 mL with an SD of 200 mL. Our sample size was calculated considering a treatment effect of 50% chosen as minimal relevant difference and 0.01 as the upper limit for type II-error. The protocol was approved by the Hospital Ethics Committee and after obtaining written informed consent, patients were randomly assigned either to the study group, where deliberate hypotension was used, or to the control group where patients were kept normotensive. The surgical procedures were performed by three different surgeons and, to avoid the possibility of bias, a specific random table was used for each of them.

Anesthetic Protocol

Patients were premedicated with oral diazepam 10–15 mg 2 hr preoperatively. On leaving the ward, they received 80 mg of methylprednisolone IV followed by an additional 80 mg every 4 hr up to a total of five doses. Four hours after the last dose of methylprednisolone was given, 100 mg of the Depomedrol® formulation of methylprednisolone was administered IM, according to a standard regimen routinely used in our institution to decrease postoperative edema (11).

In the operating room, an IV infusion of lactated Ringer's solution (LR) was started. Monitoring included electrocardiogram (ECG), urinary output, temperature, peripheral nerve stimulator, and a radial artery catheter for blood pressure monitoring and arterial blood gas analysis. Operations were carried out in a 15° Fowler position.

Induction of anesthesia was the same in the two groups: fentanyl 5 μg/kg of body weight, thiopental 5–7 mg/kg, and atracurium 0.5 mg/kg. When maximal relaxation was attained, nasotracheal intubation was performed. Respiration was controlled with an Ohio V5A ventilator and a Bain circuit. Both minute ventilation and fresh gas flow were adjusted to maintain normocapnia (Paco$_2$ 35–40 mm Hg). Anesthesia was maintained with 60% nitrous oxide in oxygen, low concentrations of isoflurane, and supplementary doses of fentanyl up to a maximum of 20 μg/kg. Before incision, the surgeon infiltrated the oral mucosa with lidocaine 2% and epinephine 1/100,000.

Deliberate hypotension was started with the mucosal incision and ended with mucosal suturing. In the hypotensive group, the inspired concentration of isoflurane was increased to lower mean arterial pres-

Table 1. Quality of Surgical Field

5. Massive uncontrollable bleeding
4. Bleeding, heavy but controllable, that significantly interferes with dissection
3. Moderate bleeding that moderately compromises surgical dissection
2. Moderate bleeding, a nuisance but without interfering with accurate dissection
1. Bleeding, so mild it was not even a surgical nuisance
0. No bleeding, virtually bloodless field

From Fromme GA et al. (10).

sure (MAP) to 55–65 mm Hg, whereas in the control group MAP was maintained at 75–35 mm Hg. Propranolol 1.0 mg IV was given if the heart rate increased over 100 beats/min. The surgical team was unaware to which group patients belonged until the end of the investigation.

At the end of surgery, patients were kept in the recovery room until fully awake and then transferred to an intensive care unit. Postoperative IV fluid regimen was 2 mL·kg^{-1}·hr^{-1}. Endotracheal tubes were removed in all patients next morning.

A strict fluid replacement protocol was followed. LR was infused intra-operatively at a rate of 6 mL·kg^{-1}·hr^{-1} with a volumetric pump to maintain routine intra-operative fluid requirements. Allowable blood loss (ABL) was defined as 20% of estimated blood volume (male 70 mL/kg, female 65 mL/kg). Blood losses up to the ABL were replaced with 3 mL of LR for each milliliter of blood lost. When blood losses reached the ABL, one unit of packed red cells was transfused and then an additional unit for every additional 400 mL of blood loss. During the procedure, the amount of irrigation fluid used was precisely measured. At the end of surgery, an investigator unaware of the patient's group evaluated blood losses by weighing the surgical sponges and precisely measuring blood and irrigation fluid in the suction containers. The surgical field was rated by the surgical team using an ordinal scale published by Fromme et al. (10) (Table 1). The surgeons were asked to evaluate the field twice: first during mucosal dissection before performing the maxillary osteotomy and again during maxillary osteotomy.

Postoperative edema was evaluated using two different methods by a member of the surgical team (still in a double blind manner). First, a subjective evaluation on a linear analogue scale graduated from 0 (no edema) to 10 (extreme edema) was made 24 hr postoperatively. Second, skin marks were placed over each patient's mandibular angles before surgery and the intermandibular distance was measured with a caliper (Figure 1). This distance was again measured

Figure 1. Measurement of the distance between skin marks placed over mandibular angles.
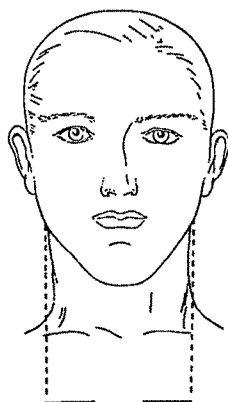
24 and 48 hr postoperatively for objective measurements. The difference between postoperative and preoperative measurements was then calculated for each patient.

All data are presented as mean ± SD. Statistical analysis was done using Student's *t*-test, ANOVA, Fischer's exact test, or the Wilcoxon rank sum test when appropriate. Differences were considered statistically significant when $P < 0.05$.

Results

Patient characteristics and clinical data are summarized in Table 2. The two groups were comparable with respect to age, weight, sex distribution, and preoperative blood pressure. There was no statistically significant difference between groups in duration of surgery. Mean duration of deliberate hypotension was 233.5 ± 64.9 min. Oliguria was significantly more frequent in the hypotensive group, but serum creatinine did not increase in either group. Mean blood loss was significantly lower in the hypotensive group as was the number of patients who had to be transfused (Table 3). The surgical field was rated significantly better in the hypotensive group both before and during maxillary osteotomy (Figure 2). Subjective and objective measurements of postoperative edema were done on 47 and 40 patients, respectively, and data are summarized in Figure 3 and Table 4. There were no statistically significant differences between the two groups at 24 or 48 hr postoperatively.

Discussion

During most orthognathic procedures, bleeding cannot be easily controlled by the surgeon. Two sources of bleeding can be identified: the first originates from

the oozing of the mucosa, the second from the osseous venous plexus opened during the osteotomies. The surgeon has relatively good control over the former but has little or no control over the latter, which seems to be the main source of blood loss. Alternative techniques have been proposed to decrease bleeding associated with the osteotomies. The head up position can have a small effect, but profuse bleeding is often a problem and patients often need transfusions (10,12).

Our data indicate that deliberate hypotension with isoflurane is an effective way to decrease blood loss in orthognathic surgery. This work is the first controlled study confirming the effectiveness of deliberate hypotension in this type of surgery. Blood losses were reduced 40%. Such a reduction, however, may not be clinically relevant unless it decreases the frequency of transfusions or provides better operating conditions. In fact these two variables were greatly improved by controlled hypotension in the present study. Blood loss exceeded ABL in only 3 patients in the hypotensive group compared with 12 patients in the control group. The high percentage of patients transfused in our control group (44%) is comparable with the data of Fromme et al. (10) (62.5% in their total population). These numbers combined with recent reports on the risks of transmission of viral diseases by blood products (13) emphasizes the need of a strategy to reduce the number of transfusions in these young patients. This young age (25.8 ± 7.0 years) decreases the potential of complications from the hypotensive technique, so the balance between advantages and risks favors the use of hypotension for this category of patients in comparison with hip or cancer surgery, where the higher incidence of cardiovascular disease may increase the risk associated with use of deliberate hypotension (14).

Operating conditions in the surgical field were also improved in our study by controlled hypotension. Most apparent during the osteotomies (Figure 2), this result suggests that deliberate hypotension is especially effective for controlling bleeding originating from bone where surgical control is poor. Benefits of a better surgical field include more accurate dissection and less tissue trauma. It is interesting to note that improvement in the surgical field did not decrease operative time. Some investigators (3,4,15) reported similar results for other types of surgery; although others (2,5,16) have found reductions in operative time.

Our results differ from those reported by Fromme et al. (10). These differences may be explained by the following factors. Fromme and co-workers used three smaller groups, which, combined with the high vari-

Table 2. Patient Characteristics and Clinical Data

	Control (N = 27)	Hypotension (N = 25)	P value
Age (yr)	26.1 ± 6.9	25.4 ± 7.1	NS[a]
Weight (kg)	61.0 ± 12.6	60.2 ± 11.1	NS[a]
Gender (m/f)	10/17	6/19	NS[b]
Preoperative Blood			
Pressure (mm Hg) systolic	114.1 ± 9.4	115.0 ± 8.4	NS[a]
diastolic	70.0 ± 7.8	70.2 ± 7.7	NS[a]
MAP during surgery (mm Hg)	80.7 ± 4.4	60.0 ± 2.3	<0.001[a]
Duration of surgery (min)	298.4 ± 65.8	274.8 ± 58.5	NS[a]
Duration of hypotension (min)	—	233.5 ± 64.9	
Inspired isoflurane (%)	0.8 ± 0.3	1.8 ± 0.9	<0.001[a]
Oliguria (no. of patients)	5	17	<0.001[b]
Creatinine variation (mMol/L)	−11.4 ± 12.1	−7.8 ± 11.3	NS[a]
(postoperative minus preoperative)	N = 20	N = 22	

[a]Student's *t*-test and ANOVA; [b]Fisher's exact test.

Table 3. Surgical Blood Loss and Transfusions

	Control (N = 27)	Hypotension (N = 25)	P value
Measured Blood Loss (mL)	755.3 ± 334.6	454.0 ± 211.3	<0.001[a]
(95% CI mean difference)	(144.0 − 458.6)		
Blood loss > ABL (no. of patients)	12	3	<0.02[b]

[a]Student's *t*-test and ANOVA; [b]Fisher's exact test. ABL = Allowable Blood Loss.

ability in blood loss, could result in a failure to detect a difference that really exists. Second, different techniques for inducing hypotension might have different effects on the vascular beds involved in maxillary osteotomies. Fromme et al. (10) used nitroprusside, which might be less effective than isoflurane in reducing blood loss in orthognathic surgery. However, this hypothesis is not currently supported by any data in the literature.

Postoperative swelling is a major concern in orthognathic surgery, but there is no report in the literature on the effect of controlled hypotension on this complication. We had two hypotheses on its possible effects on postoperative edema. Edema might be either reduced—as improving the surgical conditions would allow a more accurate and shorter dissection—or worsened by low tissue perfusion and cellular hypoxia resulting from hypotension. We could not find any effect on external edema and this might be because of the moderate number of patients studied and the large variability in postoperative edema. Another possible explanation is the blunting effect of methylprednisolone on edema formation. It has been reported to be very effective in reducing postoperative swelling in orthognathic surgery (11), which may explain our failure to detect any effect of deliberate hypotension. Also, we evaluated external
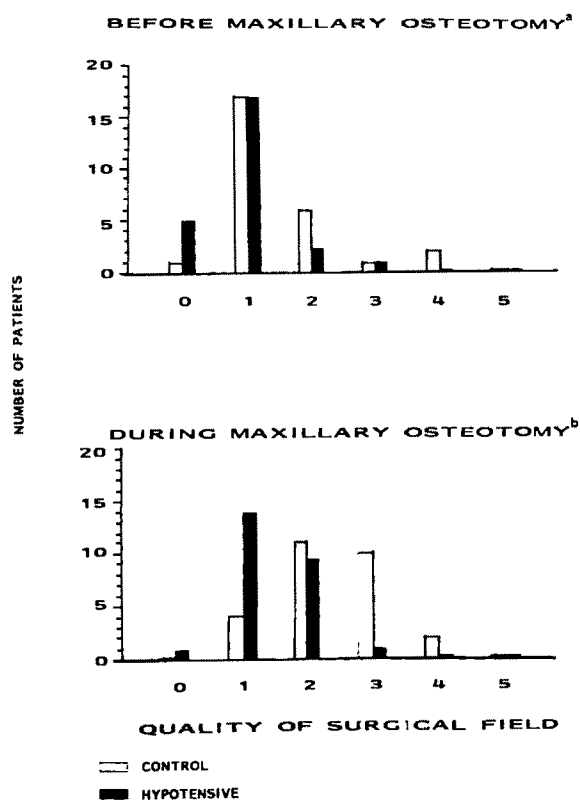
Figure 2. Evaluation of the surgical field with the scale described in Table 1 showing a better rating in the hypotensive group both before and during maxillary osteotomies. Statistical analysis with the Wilcoxon rank sum test. [a]$P < 0.05$; [b]$P < 0.001$.

edema, whereas internal edema of tongue, palate, and uvula can impair breathing and swallowing after extubation and thus be of greater clinical importance. However, it is very difficult to obtain a reliable measure of edema. We think that external edema should correlate well with internal edema, though that may not be the case. In any event, external edema is usually the only guidance to the clinician
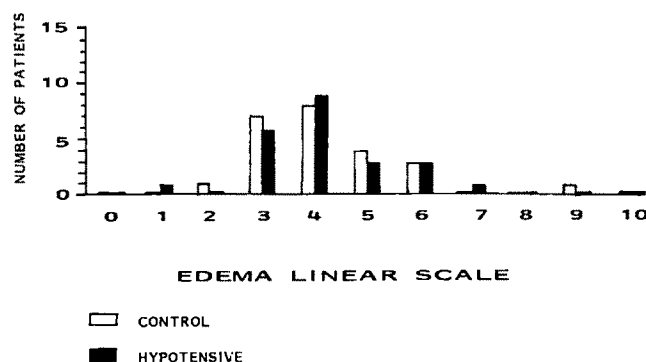
Figure 3. Subjective evaluation of external edema on a scale graduated from 0 (no edema) to 10 (extreme edema). P = NS with the Wilcoxon rank sum test.

Table 4. Postoperative Edema, Intermandibular Distance

	Control (N = 20)	Hypertension (N = 20)	
24 hr postoperative minus preoperative (mm)	13.9 ± 8.5	13.5 ± 7.3	NS[a]
48 hr postoperative minus preoperative (mm)	10.8 ± 7.6	12.3 ± 5.5	NS[a]

[a]Student's *t*-test.

before extubation because the intermaxillary fixation impairs mouth opening.

There is no report in the literature about the effect of isoflurane-induced hypotension on renal function, but our results are compatible with those of Behnia et al. (17), who found that nitroprusside-induced hypotension results in oliguria without causing kidney damage. Serum creatinine is only a gross measurement of renal function, and so the fact that serum creatinine levels remained unchanged does not allow us to conclude that our technique of hypotension is totally innocuous for the kidney. However, our patients, like Behnia's, resumed a normal diuresis shortly after the end of the hypotensive period.

We conclude that hypotension induced with isoflurane is a safe technique that reduces blood loss and transfusions (along with their related risks) and improves the quality of the surgical field in orthognathic surgery. Our results do not suggest any influence of deliberate hypotension on postoperative edema.

References

1. Griffiths HWC, Gillies J. Thoracolumbar splanchnicectomy and sympathectomy: anaesthetic procedure. Anaesthesia 1948; 3:134–46.
2. Thompson GE, Miller RD, Stevens WC, Murray WR. Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver and kidney). Anesthesiology 1978;48:91–6.
3. Grundy BL, Nash CL, Brown RH. Deliberate hypotension for spinal fusion: prospective randomized study with evoked potential monitoring. Can Anaesth Soc J 1982;29:452–61.
4. Ahlering TE, Henderson JB, Skinner DG. Controlled hypotensive anesthesia to reduce blood loss in radical cystectomy for bladder cancer. J Urol 1983;129:953–4.
5. Eckenhoff JE, Rich JC. Clinical experiences with deliberate hypotension. Anesth Analg 1966;45:21–8.
6. Ward CF, Alfery DD, Saidman LJ, Waldman J. Deliberate hypotension in head and neck surgery. Head Neck Surg 1980;2:185–95.
7. Golia JK, Woo R, Farole A, Seltzer JL. Nitroglycerin-controlled circulation in orthognathic surgery. J Oral Maxillofac Surg 1985;43:342–5.
8. Washburn MC, Hyer RL. Deliberate hypotension for elective major maxillofacial surgery: a balanced halothane and morphine technique. J Maxillofac Surg 1982;10:50–5.
9. Chan W, Smith DE, Ware WH. Effects of hypotensive anesthesia in anterior maxillary osteotomy. J Oral Surg 1980; 38:504–8.
10. Fromme GA, MacKenzie RA, Gould AB, Lund BA, Offord KP. Controlled hypotension for orthognathic surgery. Anesth Analg 1986;65:683–6.
11. Schaberg SJ, Stuller CB, Edwards SM. Effect of methylprednisolone on swelling after orthognathic surgery. J Oral Maxillofac Surg 1984;42:356–61.
12. Schaberg SJ, Kelly JF, Terry BC, Posner MA, Anderson EF. Blood loss and hypotensive anesthesia in oral-facial corrective surgery. J Oral Surg 1976;34:147–56.
13. Ward JW, Holmberg SD, Allen JR, et al. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. N Engl J Med 1988; 318:473–8.
14. Lindop MJ. Complications and morbidity of controlled hypotension. Br J Anaesth 1975;47:799–803.
15. Lawson NW, Thompson DS, Nelson CL, Flacke JW, North ER. Sodium nitroprusside-induced hypotension for supine total hip replacement. Anesth Analg 1976;55:654–62.
16. Amaranath L, Cascorbi HF, Singh-Amaranath AV, Frankmann DB. Relation of anesthesia to total hip replacement and control of operative blood loss. Anesth Analg 1975;54:641–8.
17. Behnia R, Siqueira EB, Brunner EA. Sodium nitroprusside-induced hypotension: effect on renal function. Anesth Analg 1978;57:521–6.

Ocular Lubricants and Corneal Injury during Anesthesia

Stephen E. Orlin, MD,* Fred K. Kurata, MD, Theodore Krupin, MD,* Mark Schneider, MD, Ray R. Glendrange, MD

ORLIN SE, KURATA FK, KRUPIN T, SCHNEIDER M, GLENDRANGE RR. Ocular lubricants and corneal injury during anesthesia. Anesth Analg 1989;69:384-5.

Seventy-six patients undergoing general endotracheal anesthesia were studied prospectively to determine whether simply taping the eyelids closed during the surgical procedure as opposed to taping the lids after instilling a bland lubricating ointment had any different effect on corneal or conjunctival epithelium. No significant difference was found.

Key Words: EYES, CORNEA—abrasion.

General anesthesia is occasionally complicated by injury to the eye as it causes a significant reduction in basal tear production with resultant corneal drying and possible exposure keratopathy (1). In addition, there can be direct injury to the unprotected eye during general anesthesia. There is no standard way of protecting the eye, especially the cornea, during general anesthesia. The anesthesiologist may do nothing, tape the eyelids closed, or instill a bland lubricating preparation into the eyes.

The purpose of the present study was to determine whether it is sufficient to tape the eyelids closed or whether it is necessary to instill a bland lubricating ointment into the eyes as a prophylactic measure against corneal injury during general anesthesia.

Material and Methods

Seventy-six patients undergoing general anesthesia for nonocular surgery were studied prospectively. To avoid a possible drying effect that an anesthetic gas delivered by a face mask may have on the cornea, only intubated patients were included.

Patients who had previous eye surgery, wore contact lenses, had a visual acuity worse than 20/60, or had any history of ocular disease were excluded from the study. Preoperative examination included visual acuity, slit-lamp examination using a portable slit-lamp, staining of the cornea with fluorescein and rose bengal dye, and determination of basal tear secretory rate. Fluorescein dye detects corneal epithelial loss, whereas rose bengal is a vital dye that stains devitalized epithelial cells. The basal secretory rate is an objective means of quantitating basal tear production by measuring in millimeters the amount of wetting in 5 min of a thin strip of Schirmer filter paper suspended in the lower cul-de-sac of each eye. This procedure was done to ensure that no patient had underlying dry eyes that could have predisposed them to a corneal abrasion.

At the time of general anesthesia, the anesthesiologist taped one eye shut. The other eye had a bland lubricating ointment, white petrolatum 55% (Labrilube®), instilled before taping the eyelids closed. The eye receiving the ointment was randomly selected by the anesthesiologist. This was indicated on a form that included patient identification and the length and type of operation. The envelope was sealed and unopened until completion of the study. The ointment and tape were applied only once during the procedure. The tape was removed from both eyelids when the patient was awakened.

Three to five hours postoperatively, the patients were examined at the bedside. Inquiries were made about ocular discomfort, visual acuity was measured, and the conjunctiva and cornea were examined with a portable slit-lamp with fluorescein solution and rose bengal dye. The patient received a follow-up examination at 24 hr if any abnormalities were noted on the first postoperative examination. The ophthalmologist conducting the pre- and postoperative examination was not aware of which eye had received the lubri-

cating ointment and which had simply been taped shut. The ointment had spontaneously dissolved by the first postoperative examination.

An informed consent was obtained from all the patients before the study and the study was approved by our Institutional Human Investigation Committee.

Results

The average age of the patients was 58.1 years (range 24 to 78 years), and 40 were male and 36 female. The duration of the surgical procedure was between 45 and 385 min (average 165 min). None of the patients studied had any ocular discomfort or complaints post-operatively.

The visual acuity of five patients could not be assessed in the immediate postoperative period because of depressed level of consciousness. In five patients, the visual acuity in the eye in which the ointment had been instilled was 2 to 6 lines worse than the preoperative acuity. In the remaining patients, there was no difference in the visual acuity, and in all the patients, the visual acuity returned to the baseline preoperative levels at 24 hr.

One patient showed minimal staining of the conjunctiva in the inferior cul-de-sac with both fluorescein and rose bengal dye in the eye that received no ointment; this resolved by 24 hr. The fellow eye of this patient that received lubricating ointment did not have staining with either dye. The remaining 75 patients had no evidence of corneal or conjunctival change in either eye postoperatively.

Discussion

The most frequent ophthalmic complication after general anesthesia is corneal abrasion (2,3). Fortunately, the majority of corneal abrasions resolve with instillation of antibiotic ointment and pressure patching, rarely leading to permanent ocular damage.

Corneal abrasions usually result from drying of the corneal epithelium (2). Incomplete eyelid closure and decreased basal tear production induced by the general anesthetic are the main etiologic factors responsible for corneal drying (1,4). Some corneal abrasions result from trauma. Surgical drapes may rub the eye or part of the anesthetic mask may abrade the cornea.

General anesthesia induces a significant decrease in basal tear production (1). However, our results indicate that this transient ocular state does not appear to be harmful as long as the eyelids are taped closed during general anesthesia. Only one eye not receiving ointment demonstrated a transient staining of the conjunctiva with fluorescein and rose bengal dye ($\chi^2 >$

0.7). Decreased tear production resulting from genera anesthesia does not appear to be harmful to the normal eye if the eyelids are taped closed. This may not be the situation in patients with pre-existing dry eyes and associated conjunctival and corneal defects Dry eye syndrome is frequently associated with various collagen vascular diseases including rheumatoid arthritis. In addition, decreased basal tear production occurs with increasing age and is a common finding in individuals over the age of 55 years.

Batra and Bali (4) reported an incidence of cornea abrasions in 44% of patients in whom the eyes were partly open during general anesthesia. None of the eyes that were closed during the procedure sustained corneal injury. Although the number of patients in our study was small, our results support their findings There is no clinical difference in the corneal or conjunctival epithelium in eyes that are simply taped shut, as opposed to those that are lubricated with a bland ophthalmic ointment before eyelid taping for the duration of the operative procedure. Taping the eyelids closed during general anesthesia, either with or without lubricating ointment, markedly reduces the occurance of corneal injury, as manifested by the absence of corneal epithelial loss or devitalization in our patients.

Summary

Seventy-six patients undergoing general endotrachea anesthesia for nonocular surgery were studied prospectively, in a masked fashion, to determine whether taping the eyelids closed during the surgical procedure as opposed to taping the eyelids after instilling a bland lubricating ointment had any significant effect on corneal or conjunctival epithelium. One patien showed minimal conjunctival staining, with both fluorescein and rose bengal dye, in the eye without ointment, but this cleared by the 24-hr follow-up examination. The remaining 75 patients had no evidence of postoperative corneal or conjunctival change in either eye.

References

1. Krupin T, Cross DA, Becker B. Decreased basal tear production associated with general anesthesia. Arch Ophthalmol 1977 95:107-8.

2. Terry HR, Kearns TP, Love JH. Untoward ophthalmic and neurologic events of anesthesia. Surg Clin North Am 1965 45:927-9.

3. Snow JC, Kripke BJ, Norton MG. Corneal injuries during general anesthesia. Anesth Analg 1975;54:465-7.

4. Batra YK, Bali IM. Corneal abrasions during general anesthesia Anesth Analg 1977;56:363-5.

Preinduction Atropine or Glycopyrrolate and Hemodynamic Changes Associated with Induction and Maintenance of Anesthesia with Propofol and Alfentanil

Mark A. Skues, BMedSci, BM, BS, FFARCS, Michael J. Richards, MB, BCh, FFARCS,
Anthony P. Jarvis, MB, BCh, FFARCS, and Cedric Prys-Roberts, DM, PhD, FFARCS, FFARACS

SKUES MA, RICHARDS MJ, JARVIS AP, PRYS-ROBERTS C. Preinduction atropine or glycopyrrolate and hemodynamic changes associated with induction and maintenance of anesthesia with propofol and alfentanil. Anesth Analg 1989;69:386–90.

Total intravenous anesthesia by infusions of propofol and alfentanil may be associated with decreases in heart rate and blood pressure. The effects of two vagolytic agents on these hemodynamic changes were studied in 24 ASA physical status 1 patients undergoing body surface surgery. Patients were randomly allocated to receive atropine 10 µg/kg, glycopyrrolate, 5 µg/kg, or 0.9% sodium chloride, intravenously, 5 min before induction of anesthesia with loading doses of alfentanil, 50 µg/kg and propofol 1 mg/kg. Anesthesia was maintained with infusions of alfentanil 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, and propofol 10 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the first 10 min, 8 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the next 10 min, and 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ thereafter. Patients given glycopyrrolate before anesthesia had significantly higher arterial pressures than did patients receiving either atropine or saline, even though heart rates increased equally after glycopyrrolate and atropine.

Key Words: ANALGESICS, ALFENTANIL. ANESTHETICS, INTRAVENOUS—propofol. PARASYMPATHETIC NERVOUS SYSTEM, ATROPINE, GLYCOPYRROLATE.

The pharmacokinetic profiles of alfentanil and propofol favor their combined continuous intravenous infusion during surgery (1–4). Induction and maintenance of anesthesia with a propofol infusion is associated with occasional marked decreases in systolic and diastolic blood pressures (5), particularly in the elderly patient (6). These reductions can be minimized by the use of a smaller loading dose and a computer-controlled (7) or manual infusion scheme (8) designed to maintain optimum stable whole blood propofol concentrations. We have combined such schemes with an alfentanil infusion and have determined the dose requirements of propofol for surgery (9). However, the combination of two centrally acting vagotonic agents, propofol (10) and alfentanil, de-

creased heart rates on induction, with concomitant decreases in arterial pressure.

We have therefore studied the effects of intravenous administration of two vagolytic agents, atropine and glycopyrronium (glycopyrrolate), in an attempt to modify the bradycardia and hypotension seen during induction and maintenance of anesthesia with propofol and alfentanil.

Methods

The study was approved by the Bristol District Ethics Committee and the Committee for Safety of Medicines. Twenty-four healthy ASA physical status 1 patients, aged 25–63 years and weighing 56 to 108 kg agreed to participate in the study. They were premedicated with 20–30 mg of temazepam orally, 2 hr before induction of anesthesia.

Patients were randomly allocated to one of three groups to receive either glycopyrrolate, 5 µg/kg, atropine sulphate, 10 µg/kg or 0.9% sodium chloride, intravenously, 5 min before induction. Drugs were diluted to equal volumes and administered on a

double-blind basis, followed by 5 mL 0.9% sodium chloride to flush the intravenous cannula.

Anesthesia was induced with loading doses of propofol, 1 mg/kg, and alfentanil, 50 μg/kg, given over a period of 1 min. Maintenance infusions were then started using two calibrated syringe pumps (Vickers Treonic IP4) delivering alfentanil, 50 μg·kg^{-1}·hr^{-1}, and a three-step reducing infusion of propofol, at an initial rate of 10 mg·kg^{-1}·hr^{-1} for the first 10 min, followed by 8 mg·kg^{-1}·hr^{-1} for the next 10 min, and then 6 mg·kg^{-1}·hr^{-1} thereafter. Atracurium, 0.5 mg/kg, was given immediately after the loading doses of propofol and alfentanil, but tracheal intubation was delayed for 10 min to avoid the superimposition of any hemodynamic effects of laryngoscopy during the immediate postinduction period.

Patients were ventilated with 100% oxygen through a Mapleson D system and facemask prior to intubation, and then by an Oxford ventilator delivering 10 mL/kg tidal volume of oxygen enriched air (Fi$_{O_2}$ = 0.33). End tidal carbon dioxide was measured and maintained at 4.8–5.3 KPa (36–40 mm Hg) throughout anesthesia (Engstrom Eliza Duo).

Monitoring of arterial blood pressure with an automated sphygmomanometer and ECG (CM5 configuration) were initiated before the start of the induction sequence.

At the end of surgery, spontaneous reversal of neuromuscular blockade was confirmed with a peripheral nerve stimulator, and both infusions were discontinued. The times taken to extubation, response to command, and recall of birthdate were recorded. Postoperative analgesia was given, if required, following determination of these recovery times.

All patients were seen on the first postoperative day and questioned about their experience of induction and recovery from anesthesia.

Population characteristics were compared using the Kruskal-Wallis test statistic. Analysis of variance with two-tailed unpaired t-tests with correction for the Bonferroni inequality (11) were used to evaluate differences in heart rate and blood pressure between the groups. The total doses of drugs administered to each patient were calculated and compared with the indices of recovery using standard correlation analysis techniques. Recovery times were subjected to logarithmic transformation to correct for positive skewness before analysis.

Results

There were no significant differences in patient age, weight, sex ratio, or duration of infusion in the three groups studied (Table 1).

Table 1. Population Characteristics and Duration of Infusion

	Saline	Glycopyrrolate	Atropine
Age (years)	45.6	40.0	42.1
	±11.6	±7.6	±10.7
Weight (kg)	69.1	73.9	74.6
	±11.3	±13.2	±8.7
M/F Ratio	5:3	6:2	6:2
Duration of infusion (min)	61 (36–87)	80 (30–96)	64 (37–125)

Values for age and weight expressed as mean ± standard deviation. Values for duration of infusion expressed as median and (range).

Hemodynamic values were similar in the three groups before administration of any drugs ($P > 0.05$). Heart rate increased significantly ($P < 0.001$) during the 5 min before induction in patients given glycopyrrolate or atropine and remained significantly higher during maintenance of anesthesia than in patients receiving normal saline (Figure 1).

Patients given glycopyrrolate before induction had significantly higher ($P < 0.05$) systolic and diastolic blood pressures for the first 10 min after induction compared with those receiving atropine or saline. These differences were not significant ($P > 0.05$) after laryngoscopy and intubation at 10 min (Figures 2 and 3).

Recovery times for patients given atropine before induction were longer but not statistically significantly so when compared with the saline and glycopyrrolate groups (Table 2). There was no correlation between the total doses of propofol and alfentanil given and the recovery times.

None of the patients recalled any events during surgery, and all were satisfied with the quality of anesthesia and recovery. One patient given glycopyrrolate reported nausea within the first 6 hr of recovery; otherwise no patients developed nausea or vomiting. One patient in the glycopyrrolate group complained of an excessively dry mouth postoperatively.

Discussion

The combination of propofol and alfentanil fulfills the majority of the requirements for a total intravenous anesthetic technique (12). This study demonstrates that the administration of glycopyrrolate before induction and maintenance with these agents significantly attenuates the initial decreases in heart rate and blood pressure, ensuring hemodynamic stability. The surprising feature was that an equipotent dose of atropine had no effect on the decrease in blood pressure seen with induction of anesthesia.
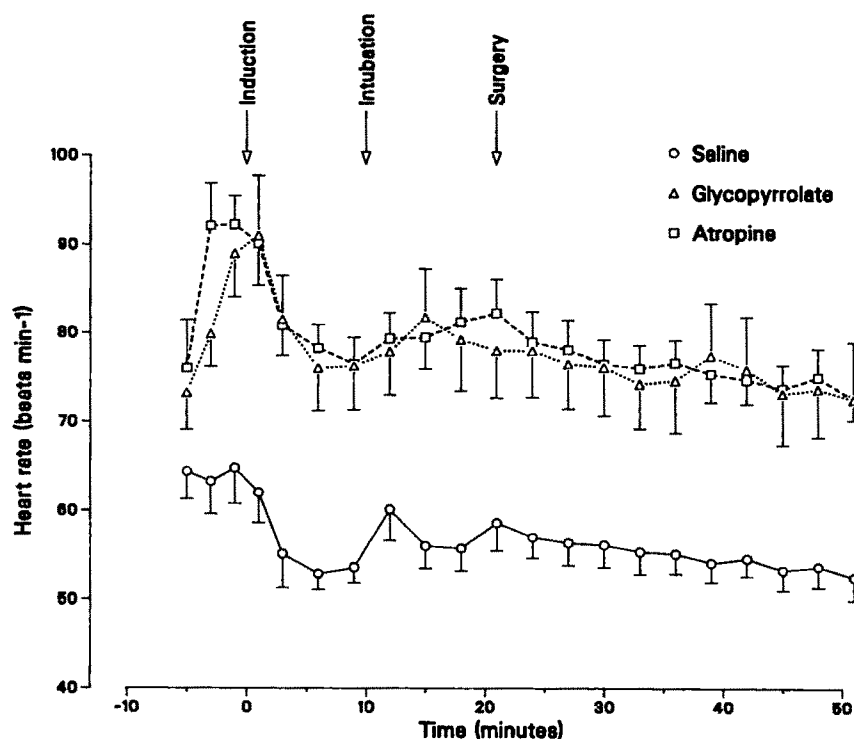
Figure 1. Heart rates in patients given saline, glycopyrrolate, or atropine.
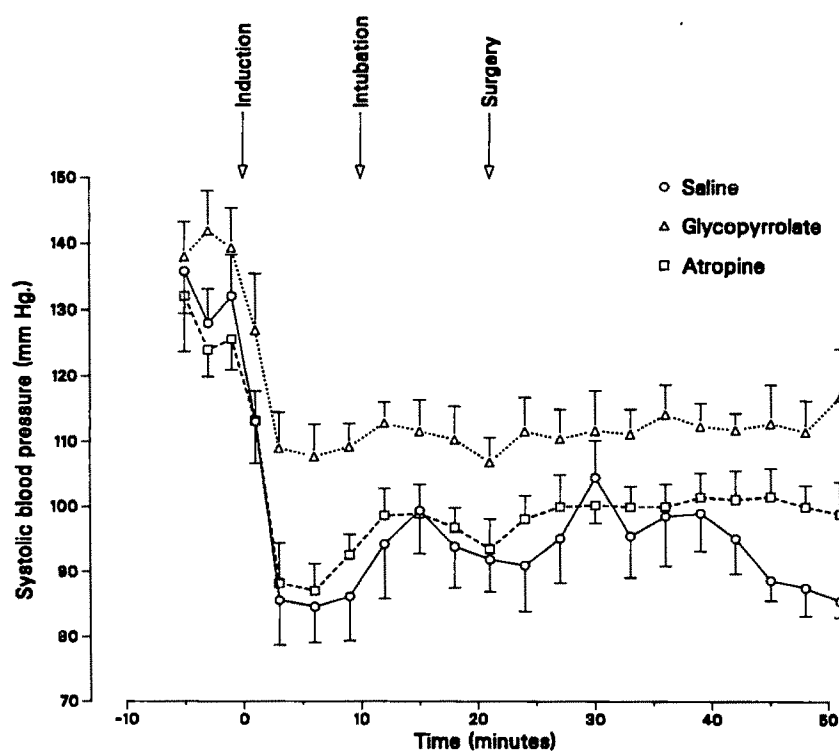
Figure 2. Systolic blood pressures in patients given saline, glycopyrrolate, or atropine.

The doses of anticholinergic agent employed in the study were chosen after reference to previously published data concerning both equipotency in effect on heart rate (13) and dose requirements consistently to increase heart rate (14).

The cardiovascular effects of large and small doses of atropine have been extensively studied in both awake and anesthetized patients. Changes in blood pressure following atropine administration are variable, with reports of both hypo- and hypertension. In

Figure 3. Diastolic blood pressures in patients given saline, glycopyrrolate, or atropine.
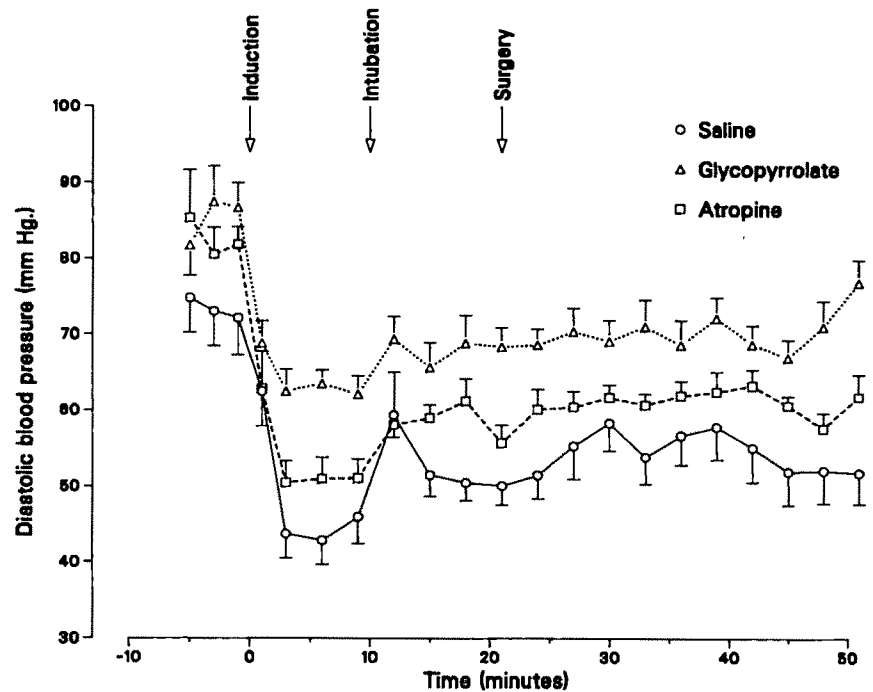
Table 2. Recovery Times after Discontinuation of Infusions

	Saline	Glycopyrrolate	Atropine
Extubation (min)	14	14	17
	(3–24)	(11–21)	(15–22)
Response to command (min)	15	15.5	18
	(4–25)	(12–21)	(15–35)
Recall of date of birth (min)	15.5	16	18.5
	(4–28)	(12–21)	(16–37)

Values expressed as median and (range).

the awake, supine subject, atropine increases cardiac output and mean arterial pressure concomitant with the tachycardia, together with a decrease in central venous pressure and systemic vascular resistance (15). Tilting the subject into an upright position after administration of atropine results in marked postural hypotension with little or no reflex compensation (16). It therefore appears that blood pressure changes after atropine administration are dependent upon the balance between an increase in cardiac output as a consequence of the chronotropic action, and an associated decrease in systemic vascular resistance as a result of presumed partial ganglionic blockade (17).

All data available on the hemodynamic consequences of administration of glycopyrrolate suggest that any changes in blood pressure changes are so minimal as to be statistically insignificant (13,18–21). However, our findings in no way contradict the results of previous studies as they were derived

during anesthesia with alfentanil and propofol, the latter being unique among anesthetic agents in its action on cardiovascular control mechanisms (10).

It is unlikely that the unique effect of glycopyrrolate in attenuating decreases in blood pressure following propofol and alfentanil is centrally mediated as glycopyrrolate crosses the blood brain barrier poorly (22). A peripheral effect on systemic vascular resistance is suggested by the equal changes in both systolic and diastolic pressures, and work is underway in this department to validate this impression.

The reason why glycopyrrolate, but not atropine, attenuates the decreases in blood pressure associated with propofol and alfentanil infusion anesthesia is unknown. There is evidence that selective muscarinic agonists can produce marked increases in arterial pressure in vivo (23) by their action on sympathetic ganglionic M_1 receptors, an effect that can be competitively antagonized by atropine (24). If glycopyrrolate exerts a selective antagonism of M_2 receptors, as opposed to the established antagonism of both M_1 and M_2 receptors by atropine (24), then one may be able to explain the difference observed. However, paucity of data concerning the receptor selectivity of glycopyrrolate means that this hypothesis must remain speculative.

The differences in recovery times, although not statistically significant, are in accord with the studies of Baraka et al. (25) and Sheref (26), who found recovery to be more rapid in patients given neostigmine and glycopyrrolate to antagonize neuromuscu-

lar blockade than in those given neostigmine plus atropine. It testifies to the exceptional recovery profile of patients receiving propofol and alfentanil that these differences were still evident almost one hour after administration of a vagolytic agent.

In conclusion, glycopyrrolate attenuates the hemodynamic response to induction of anesthesia with propofol and alfentanil by mechanisms as yet unknown. We recommend its use in this context as an adjunct in the provision of a total intravenous anesthetic technique that provides satisfactory anesthesia with a recovery that is both rapid and uneventful.

References

1. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. Br J Anaesth 1986;58:1075-9.

2. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate infusion in humans. Anesth Analg 1987;66:1256-63.

3. Hull CJ. The pharmacokinetics of alfentanil in man. Br J Anaesth 1983;55(Suppl. 2):157S-64S.

4. Fragen RJ, Booij LHDJ, Braak GJJ, Vree TB, Heykants J, Crul JF. Pharmacokinetics of the infusion of alfentanil in man. Br J Anaesth 1983;55:1077-81.

5. Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction (comparison of the effects of thiopentone and propofol). Anaesthesia 1985;40:735-40.

6. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. Br J Anaesth 1987; 59:954-60.

7. Tackley RM, Lewis GTR, Prys-Roberts C, Boaden RW, Harvey JR. Computer controlled infusion of propofol. Br J Anaesth 1989;62:46-53.

8. Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia. A manual infusion scheme. Anaesthesia 1988;43:14-17S.

9. Richards MJ, Skues MA, Jarvis AP, Prys-Roberts C. Total I.V. anaesthesia with propofol and alfentanil: Dose requirements for propofol. Br J Anaesth 1988;61:510P.

10. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115-20.

11. Glantz SA. Primer of Biostatistics. 2nd ed. New York: McGraw-Hill, 1987:88-90.

12. Morgan M. Total intravenous anaesthesia. Anaesthesia 1983; 38:1-9S.

13. Mirakhur RK, Jones CJ, Dundee JW. Effects of intravenous administration of glycopyrrolate and atropine in anaesthetised patients. Anaesthesia 1980;35:277-81.

14. Berger J, Gravenstein J, Van Der Aa J, Paulus L, Sabah-Maren E, McLaughlin G. Comparative potency of atropine sulphate and glycopyrrolate on heart rate in man. Eur J Anaesthesiol 1988;5:23-30.

15. Berry JN, Thompson Jr HK, Miller DE, McIntosh HD, Durham NC. Changes in cardiac output, stroke volume and central venous pressure induced by atropine in man. Am Heart J 1959;58:204-13.

16. Miller RD, Kalser MH, Frye CW, Gordor AS. Measurement of atropine-induced vascular pooling. Circulation 1954;10:423-9.

17. Eger EI. Atropine, scopolamine and related compounds. Anesthesiology 1962;23:365-83.

18. Miller F. Fetal and maternal cardiovascular effects of atropine and glycopyrrolate. Anesth Analg 1983;62:426-30.

19. Mirakhur RK, Dundee JW. Comparison of the effects of atropine and glycopyrrolate on various end organs. J Royal Soc Med 1980;70:727-30.

20. Oduro KA. Glycopyrrolate methobromide. 2. Comparison with atropine sulphate in anaesthesia. Can Anaesth Soc J 1975;22:466-73.

21. Murad SHN, Conklin KA, Tabsh KMA, Erinkman CR, Erkkola R, Nuwayhid B. Atropine and glycopyrrolate: Hemodynamic effects and placental transfer in the pregnant ewe. Anesth Analg 1981;60:710-14.

22. Proakis AG, Harris G. Comparative penetration of glycopyrrolate and atropine across the blood-brain barrier and placental barriers in anesthetized dogs. Anesthesiology 1978;48:339-44.

23. Roszkowski AP. An unusual type of sympathetic ganglionic stimulant. J Pharmacol Exp Ther 1961;32:156-70.

24. Hammer R, Giachetti A. Muscarinic receptor subtypes: M1 and M2 biochemical and functional characterization. Life Sci 1982; 31:2991-8.

25. Baraka A, Yared P, Karam AM, Winnie A. Glycopyrrolate-neostigmine and atropine-neostigmine mixtures affect postanesthetic arousal times differently. Anesth Analg 1980; 38:431-4.

26. Sheref SE. Pattern of CNS recovery following reversal of neuromuscular blockade. Comparison of atropine and glycopyrrolate. Br J Anaesth 1985;57:188-91.

Special Article

Theodore Dreiser's "Laughing Gas"

A. J. Wright, MLS

WRIGHT AJ. Theodore Dreiser's "laughing gas."
Anesth Analg 1989;69:391-2.

Around World War I, American novelist Theodore Dreiser wrote several plays, one of which, "Laughing Gas," explores the odd experience of a physician undergoing surgery

with nitrous oxide/oxygen anesthesia. The content of this play and its relationship to Dreiser's career are examined.

Key Words: HISTORY, THEODORE DREISER. ANESTHETICS, GASES—nitrous oxide.

In this century the physician and the hospital environment have become ubiquitous in American popular culture; doctors appear as main characters in many films (1), detective fiction (2), and television programs (3). A recent novel even features an anesthesiologist as the protagonist (4). However, despite this wealth of material, fictional descriptions of the anesthetic state from the viewpoint of the patient—especially a physician-patient—are almost nonexistent.

The various mental states associated with anesthetic gas inhalation have fascinated philosophers, poets, and other literary figures since the beginning of the 19th century. Robert Southey, Peter Mark Roget, and apparently Samuel Taylor Coleridge, for example, along with several lesser known individuals participated in Humphrey Davy's "first controlled scientific exploration of a consciousness-altering drug" in 1799 and 1800 (5). Throughout the 19th and into the 20th centuries, people as eminent as Benjamin Paul Blood, William James, Oscar Wilde, Julian Symonds, Oliver Wendell Holmes, and J.M. Synge wrote about their startling, "mystical" experiences during anesthesia (6). Writer Carl Van Vechten noted the extreme case of "a fellow novelist who became so obsessed with the elusive nature of this experience

that he had a tank of nitrous oxide installed in his basement and employed a nurse to give it to him. He took it day after day. Each time he went under, the mystic and awful explanation was vouchsafed him. But invariably, when he gained consciousness, he could no longer remember what it was" (7).

An American author who used this effect of anesthetics for his own fictional portrait of a physician undergoing anesthesia was Theodore Dreiser (1871–1945), perhaps best known for his naturalistic novels, *Sister Carrie* (1900) and *An American Tragedy* (1927). However, Dreiser was also attracted early in his career to the theater and not only worked as the drama critic for the St. Louis *Globe-Democrat* from late 1893 until early 1894, but in 1913, he wrote his first play, the one act, "The Girl in the Coffin." "He had persisted in his earliest belief that the dramatic form was the 'most natural' for him," one of his biographers has written (8). Over the next 2 years, Dreiser wrote six additional short plays that were published as *Plays of the Natural and Supernatural* in 1916. One of those works, "Laughing Gas," is of interest as perhaps the only American drama using administration of anesthesia, and the nonclinical effects of an anesthetic as major elements in its story (9).

"Laughing Gas" is a curious mixture of the realistic and the fantastic into what Keyssar has called one of Dreiser's "folk dramas" in which "the importance and richness of the lives of ordinary folk" are displayed (10). The play is set in an operating room of Michael Slade Hospital. Fenway Bail, described in Dreiser's stage notes as "a celebrated surgeon," has

arrived to remove a tumor from the neck of Jason James Vatabeel, "an eminent physician." Bail describes Vatabeel as "A remarkable man, very. Such sacrifices for his profession! How persistently he has scorned money. Great, and poor—that is my idea of a physician."

For this "minor operation," Bail has chosen nitrous oxide as the anesthetic, a choice of which Vatabeel approves. "Far be it from me to demand ether. I dislike the stuff intensely," he says. "The last time I took ether I had a very strange experience or dream, one of the best of the etheric variety, I fancy."

The nitrous oxide, "at one-fourth strength to begin with," is administered by Franklin Dryden, a physician anesthetist. As he breaths the gas, Vatabeel ruminates on the recent progress in medicine. "It hasn't been ten years since we had to administer ether and gas full strength because we didn't know how to dilute them. And there weren't any anesthetists."

The remainder of "Laughing Gas" describes Vatabeel's encounter with various anthropomorphic spirits, including that of nitrous oxide, Demyaphon. Vatabeel notes that "This is the same place I was in when I was operated on before. These are the same people." As the oxygen runs low and Vatabeel nears death, the spirits, shadows, voices, and a mantric "rhythm of the universe" lead him through a miniature "dark night" of the soul. Finally, the operation is completed, and Vatabeel, laughing maniacally, is revived. "I have the answer!" he cries. "I see the trick. The folly of medicine! The folly of life!" Vatabeel has realized that, although man is often buffeted by forces beyond his control or understanding, he struggles to live and hope. "While the mode is comic, the gesture is the classic one of religious faith" (11).

Dreiser considered "Laughing Gas" to be "the best thing I ever did," a lapse in judgement no doubt influenced by the fact "he was throughout his life strongly haunted by premonitions and omens" (8). The play "is a good example of Dreiser's metaphorical transformation of laboratory science into speculative drama" and reflects his philosophy that the material and mental worlds were inextricably mixed (11).

"Laughing Gas" was first published in The Smart Set magazine in February 1915. According to Dreiser, 2 months later he became familiar with a work by Benjamin Paul Blood, The Anaesthetic Revelation (12) and "On Some Hegelisms," Williams James' essay in which he mentions Blood's writing (13). During the 19th century, Blood spent 20 years or more experimenting with nitrous oxide and developed an elabo-

rate mystical philosophy based on those experiences. Dreiser was impressed enough with Blood's work to append it and James' comments to the 1916 second printing and 1926 republication of Plays of the Natural and Supernatural (11).

Like his other one act plays, Dreiser's "Laughing Gas" never reached the stage. The only Dreiser play ever produced was his one full-length drama, The Hand of the Potter, which appeared at the Wharf Theatre in Provincetown, Massachusetts during the 1921–22 season. However, Dreiser later managed to squeeze $300 for the original "Laughing Gas" manuscript from Robert Moody, a Milwaukee businessman who collected the author's first editions and manuscripts (14).

Despite the fact that they were never produced, Dreiser's plays influenced several prominent American dramatists, including Elmer Rice and Thornton Wilder (15). And "Laughing Gas" leaves us with a fascinating, if highly unusual, portrait by a great American author of anesthesia administration at the beginning of the 20th century.

References

1. Shale R. Images of the medical profession in the movies. Ohio State Med J 1984;80:775–9.

2. Scarlett EP. The doctor in detective fiction with an expanded note on Dr. John Thorndyke. Arch Intern Med 1966;118:180–6.

3. Turow J. Playing Doctor: Television, Story-Telling, and Medical Power. New York: Oxford University Press, 1989.

4. Welt E. Berlin Wild. New York: Viking, 1986.

5. Hoover SR. Coleridge, Humphrey, Davy and some early experiments with a consciousness-altering drug. Bull Res Human 1978;81:9–27.

6. Wright AJ, Aldrete JA. Patient memories of anesthesia: an historical perspective. Middle East J Anesth 1987;9:233–54.

7. Clendening L. Behind the Doctor. New York: Knopf, 1933:313.

8. Matthiessen FO. Theodore Dreiser. Westport, Conn.: Greenwood, 1973:175–6.

9. Dreiser T. "Laughing Gas." In Dreiser T: Plays of the Natural and Supernatural. New York: AMS Press, 1969:85–118.

10. Keyssar H. Theodore Dreiser's dramas: American folk drama and its limits. Theatre J 1981;33:365–76.

11. Boren LS. William James, Theodore Dreiser and the "anaesthetic revelation." Amer Studies 1983:24:5–17.

12. Blood BP. The Anaesthetic Revelation and The Gist of Philosophy. New York, privately printed, 1874.

13. James W. On some Hegelisms. In: James W. The Will To Believe And Other Essays In Popular Philosophy. New York: 1956:263–96.

14. Swanberg WA. Dreiser. New York: Charles Scribner's, 1965: 267–8.

15. Bigsby CW. A Critical Introduction To Twentieth-Century American Drama. I. 1900–1940. Cambridge University Press, 1982:128, 258.

Clinical Reports

Incidental Discovery of Persistent Left Superior Vena Cava during Cardiac Surgery

David L. Tomlinson, MD, Hiroshi Goto, MD, James C. Graf, MD, and Kasumi Arakawa, MD, PhD

Pulmonary artery catheterization is commonly employed before open heart surgery. Catheter location is determined by cardiac chamber and pulmonary artery pressures. A chest roentgenogram that can confirm catheter position is usually not obtained until the postoperative period.

The following is a case of pulmonary arterial catheterization through an unsuspected persistent left superior vena cava (PLSVC). Although without complications in this instance, anesthesiologists should not only be aware of how easy it is to miss the diagnosis of PLSVC when pulmonary artery catheters are inserted, but also how to recognize the abnormality on roentgenograms and how complications may arise due to arrhythmias. The diagnosis was made intraoperatively at the time of vena caval cannulation when the right superior vena cava (RSVC) was noted to be absent. Catheter position was confirmed by chest roentgenogram in the postoperative period.

Case Report

A 58-year-old man presented to the emergency ward with a 2-day history of confusion. A computed tomographic examination of the head revealed a left parietal cerebrovascular accident. At the time of admission the electrocardiogram showed atrial fibrillation and an echocardiogram was made to rule out embolism as a cause of the cerebrovascular accident. The echocardiogram revealed severe mitral stenosis. Neurosurgical consultation recommended that cardiac catheterization and possible mitral surgery be delayed for 6 weeks. Six weeks after the cerebrovascular accident, a cardiac catheterization via the femoral artery and vein was performed. Severe mitral stenosis was demonstrated with a mitral valve area of 0.7 cm^2. There was a 13-mm Hg gradient across the valve and the cardiac output was 3.25 L/min. There was no suggestion of abnormal cardiovascular anatomy.

Based on these findings, the patient was scheduled for an elective open mitral commissurotomy. After induction of general anesthesia, a 7F pulmonary artery catheter was introduced through the right internal jugular vein. The catheter was floated to the pulmonary capillary wedge position without difficulty. The catheter passed quite easily and at the time of placement there was no suspicion that the catheter might be taking an anomalous course. Before initiation of cardiopulmonary bypass, the inferior vena cava was cannulated without difficulty. An attempt was made to cannulate what was thought to be the RSVC but this proved to be impossible. It was then noted that the RSVC was absent and a PLSVC presumably draining into the coronary sinus was present. To facilitate venous drainage, a separate vent was placed in the right atrial appendage. The remainder of the procedure was uneventful and the patient was successfully weaned from cardiopulmonary bypass. The cardiac rhythm at the conclusion of cardiopulmonary bypass was regular sinus rhythm.

The postoperative anteroposterior chest roentgenogram confirmed the intraoperative findings of an absent RSVC and a PLSVC emptying into the coro-

Figure 1. Anteroposterior roentgenogram of the chest showing pulmonary artery catheter darkened by dashed lines. The catheter follows a course from the right internal jugular vein through the persistent left superior vena cava coursing through the coronary sinus, the right atrium, right ventricle, and into the right pulmonary artery.

nary sinus (Figure 1). The patient maintained sinus rhythm during the postoperative period and he was discharged from the hospital on digoxin, procainamide, nitropaste, and prazosin.

Discussion

The incidence of PLSVC has been reported in approximately 0.5% of the population (1). A PLSVC in the absence of the RSVC is much less common, where the incidence has been reported to be 0.1% (2,3). The incidence of a PLSVC when a RSVC is present may be underestimated because it may go undetected with the use of the right internal jugular and subclavian veins for invasive monitoring. The incidence of PLSVC is more common in patients with congenital heart disease where the incidence is 2% when there is situs solitus; the incidence may be as high as 40% when there is abnormal situs (2).

A detailed description of this venous anomaly has been discussed elsewhere (4). Embryologically, a PLSVC develops when the left anterior cardinal vein fails to regress. The resultant left superior vena cava usually drains into a dilated coronary sinus which empties into the right atrium. In rare occasions, the PLSVC drains directly into the left atrium. Absence of the RSVC occurs when the left cardinal vein persists and the right cardinal vein becomes rudimentary.

The postoperative anteroposterior chest roentgenogram reveals the atypical course of the pulmonary

artery catheter. The catheter can be seen on the left side of the vertebral column as it courses through the PLSVC. At the level of the cardiac base, the catheter crosses the midline obliquely via the coronary sinus. The coronary sinus orifice is located inferiorly on the posterior medial wall of the right atrium and posterior to the orifice of the tricuspid valve. As the catheter enters the right atrium it should enter the tricuspid valve anterior to the coronary sinus orifice (5). This causes the acute bend in the catheter as seen on the chest roentgenogram.

A PLSVC does not itself cause hemodynamic alterations but may be associated with various intracardiac defects including both cyanotic and acyanotic types (4). It is also important to note that patients with PLSVC could have conduction abnormalities. Lenox et al. (2) reviewed arrhythmias in 11 patients with an absent RSVC and PLSVC. Ten of the 11 patients were adults with a conduction disturbance necessitating a pacemaker. James et al. (6) made a detailed study of two adolescent patients with PLSVC. One died suddenly and the other died of an arrhythmia 16 days after repair of a ventricular septal defect. Both patients proved to have atrioventricular (AV) nodes that were fragmented and stretched over a large coronary sinus. There was also disorganization and fetal dispersion of the conduction tissue throughout the AV node and bundle of His. Conduction disturbances may be related to the close proximity of the atrioventricular node to the os of the coronary sinus. Enlargement of the coronary sinus which occurs with a PLSVC may stretch atrioventricular junctional tissue leading to arrhythmias (7).

Fraser and associates (8) reported an increased incidence of arrhythmias during cardiac catheterization when the PLSVC was used. There was a 7.9% incidence of supraventricular tachycardia (SVT) when the catheter was passed down the RSVC. This is in contrast to a 38% incidence of SVT when the PLSVC was used.

Rubenfire et al. (9) suggest that flow-directed balloon catheters will enter the pulmonary artery independent of anomalous venous connections as long as the pressure–flow relationships are favorable. They attribute the difficulty in catheterizing the pulmonary artery and the subsequent arrhythmias to the stiff non–flow-directed catheters used during cardiac catheterization. The pulmonary artery catheter in this case was floated to the pulmonary artery without difficulty. This, however, is not always true as evidenced by a case reported by Fallerick (10). He reported some difficulty with entry and transit through the right ventricle even though the catheter was a balloon-tipped pulmonary artery catheter.

It is important for those anesthesiologists who utilize pulmonary artery catheters to be aware of the roentgenographic appearance of antegrade passage of a pulmonary artery catheter through a PLSVC. Retrograde catheterization of a PLSVC can also occur (11). This anteroposterior roentgenogram will show the catheter entering the coronary sinus (from the right atrium via a RSVC) coursing its way caudad in a PLSVC and stopping with the distal end in what appears to be the left upper lung segment.

In summary, a relatively rare cardiac anomaly of PLSVC in the absence of the RSVC was discovered at the time of venous cannulation before cardiopulmonary bypass. A PLSVC alone is not hemodynamically significant. One must, however, be aware of the association with other congenital cardiac anomalies and alterations in the cardiac conduction system that may lead to arrhythmias. The presence of a PLSVC is not always apparent at the time of pulmonary artery catheter insertion. For this reason, the anesthesiologist should be aware of this cardiac anomaly, recognize it on chest roentgenogram, and be prepared to treat problems that may arise.

References

1. Steinberg I, Dubilier W, Lukas DS. Persistence of left superior vena cava. Dis Chest 1953;24:479–88.
2. Lenox CC, Zuberbuhler JR, Park SC, et al. Absent right superior vena cava with persistent left superior vena cava: Implications and management. Am J Cardiol 1980;45:117–22.
3. Boyes R, Puri VK. Absent right superior vena cava. Intensive Care Med 1984;10:45–6.
4. Campbell M, Deucher DC. The left-sided superior vena cava. Br Heart J 1954;16:423–39.
5. Coblentz MG, Criscito MA, Cohn JD. Persistent left superior vena cava complicating hemodynamic monitoring catheterization. Crit Care Med 1978;6:32–5.
6. James TN, Marhsall TK, Edwards JE. Cardiac electrical instability in the presence of a left superior vena cava. Circulation 1976;54:689–97.
7. Lembo CM, Latte S. Persistence of a left superior vena cava: a case report. Angiology 1984;35:58–62.
8. Fraser RS, Dvorkin J, Rossall RE, Eidem R. Left superior vena cava. Am J Med 1961;31:711–6.
9. Rubenfire M, Evangelista J, Wajszczuk WJ, Kantrowitz A. Implication of a persistent left superior vena cava in transvenous pacemaker therapy and cardiac hemodynamic monitoring. Chest 1974;65:145–7.
10. Falltrick RT. Pulmonary arterial catheterization through a persistent left superior vena cava. Anesthesiology 1979; 50:155–6.
11. Sprague DH, Sherwood HL. Retrograde cannulation of a persistent superior vena cava. Anesthesiology 1980;53:268.

Pseudothrombocytopenia in an Elderly Preoperative Patient

Robert C. Lavender, MD, James S. Salmon, MD, and William E. Golden, MD

Key Words: Blood, PLATELETS—thrombocytopenia.

Thrombocytopenia is generally a contraindication to elective surgical intervention. Diagnostic work-up of this disorder frequently involves a bone marrow aspiration and almost certain delay of the operation. Pseudothrombocytopenia is an uncommon laboratory artifact that can cause unnecessary testing, delay of surgery, prolonged hospital stays, and potentially harmful treatment. We report a case of pseudothrombocytopenia secondary to ethylenediaminetetraacetic acid (EDTA) induced platelet clumping in an elderly preoperative patient.

Report of a Case

An 87-year-old white woman was seen by the general medical consultant before elective total hip arthroplasty. The orthopaedic service had cancelled her surgery because of thrombocytopenia.

The patient was in good health for her age with a past medical history significant for hypertension and mild congestive heart failure. Medications included furosemide 40 mg daily, nifedipine 10 mg three times daily, and naproxen 375 mg twice daily. The patient denied any recent exacerbation of her heart failure, recent viral symptoms, bleeding or bruising tendencies, hemoptysis, hematochezia, and melena.

Physical examination revealed an elderly white female who appeared younger than her stated age. Vital signs were normal. Skin examination was normal and no petechiae were present. Cardiac examination showed no enlargement but frequent ectopic beats. There was a grade II/VI systolic ejection murmur maximum at the left sternal border without radiation; no gallops were noted. The remainder of the physical examination was within normal limits.

Electrocardiogram (ECG) was normal except for frequent premature atrial beats. Chest x-ray, arterial blood gas tensions and concentrations of electrolytes, blood urea nitrogen, and creatinine were normal. Automated cell count from venous blood collected in an EDTA test tube showed a hemoglobin of 14.0 g/100 mL and a white blood cell count of 7.4/cu.mm. with a normal differential. The platelet count was reported at 28,000/mm^3. Another blood sample was obtained for a platelet count that was reported at 15,000/mm^3. The peripheral smear showed clumped platelets. EDTA induced platelet clumping was considered and a venous sample was collected in a 3.8% sodium citrate tube and the platelet count from that specimen was 110,000/mm^3. Review of that peripheral smear showed no platelet clumping.

The patient's surgery was rescheduled for the following morning and performed without complications. The surgical site showed no abnormal bleeding. Subsequent complete blood counts during her postoperative course drawn in EDTA tubes consistently reported thrombocytopenia.

Discussion

Pseudothrombocytopenia is an uncommon phenomenon due to laboratory artifact, which if unrecognized may result in misdiagnosis and unnecessary treatment. In this condition, even though the patient has normal numbers of functioning platelets, automated cell counts indicate moderate to severe thrombocytopenia. Although artifactual thrombocytopenia may be due to sampling errors, platelet satellitosis, and cold agglutinins, the major cause appears to be from platelet clumping induced by EDTA (1). Retrospective investigation of large numbers of automated cell counts has shown the incidence of EDTA induced platelet clumping to be from 0.9% to 1.9% for specimens in outpatients and inpatients respectively (1). This phenomenon has led to unnecessary bone marrow examinations, inappropriate diagnosis of idiopathic thrombocytopenic purpura, the unnecessary use of steroids, and even splenectomy (2).

Disodium and tripotassium EDTA are chelating agents used as anticoagulants in sampling tubes used for cell counts. The mechanism by which EDTA induces platelet clumping appears to occur through antibodies that depend on EDTA for their activity. Pegels et al. (2) demonstrated clumping of normal donor platelets preserved in EDTA when incubated with the sera from patients that contained EDTA dependent antibodies (2). Interestingly, no clumping was exhibited by donor platelets in the absence of EDTA or with EDTA preserved platelets from patients with Glanzmann's disease. From these findings, it has been speculated that the antibodies may be cross-reacting antibodies directed against a naturally occurring chemical substance related to EDTA or that EDTA in some manner exposes hidden antigenic determinants of platelet membrane glycoproteins IIB or IIIA, glycoproteins missing from the platelets in Glanzmann's disease. The antibodies involved are most commonly IgG, but IgA and IgM antibodies have also been implicated (2). One study (3) using immunoblotting and crossed immunoelectrophoresis has shown that the IgM antibody in a patient with pseudothrombocytopenia reacted with platelet glycoprotein IIB.

The diagnosis of pseudothrombocytopenia should be suspected in patients lacking stigmata of thrombocytopenia. Pseudoleukocytosis may also be seen because automated cell counters may interpret the platelet clumps as leukocytes (4). Although newer instruments using leukocyte histograms or leukocyte peroxidase X-Y displays may alert the technician to the possibility of platelet clumping, simple examination of the peripheral blood smear will show the presence of platelet clumps. Establishment of EDTA as the causal agent can be made by resampling venous blood using test tubes containing heparin or 3.8% sodium citrate. Review of the peripheral smear from these tubes should reveal no platelet clumping, and the platelet count will be higher than the count from the EDTA tube. The platelet count determined by these two methods will be somewhat lower than the actual platelet count because of dilution by the anticoagulants. Payne and Pierre (1) describe another technique by which blood can be collected using an ammonium oxalate unopette and cell count performed using phase microscopy. Again, no platelet clumps should be observed and the count should be higher than that when EDTA is used.

In the present case, prompt recognition of pseudothrombocytopenia avoided cancellation of surgery and an expensive diagnostic workup in an otherwise healthy elderly patient.

References

1. Payne BA, Pierre RV. Pseudothrombocytopenia: a laboratory artifact with potentially serious consequences. Mayo Clin Proc 1984;59:123–5.

2. Pegels JG, Bruynes EC, Engelfriest CP, Von-dem-Borne AE. Pseudothrombocytopenia: an immunologic study on platelet antibodies dependent on ethylene diamine tetra-acetate. Blood 1982;59:157–61.

3. Van-Vliet HH, Kappers-Klunne MC, Abels J. Pseudothrombocytopaenia: a cold autoantibody against platelet glycoprotein GPIIB. Br J Haematol 1986;62:501–11.

4. Savage RA. Pseudoleukocytosis due to EDTA induced platelet clumping. A J Clin Path 1984;81:317–22.

Celiac Plexus Block for Hepatic Arterial Embolization: A Comparison with Intravenous Morphine

Keith A. Loper, MD, Douglas M. Coldwell, MD, PhD,* John Lecky, MD, and
Catherine Dowling, MD

Hepatic arterial embolization (HAE) provides symptomatic palliation for patients with unresectable primary and metastatic hepatic malignancies (1). The procedure involves the selective embolization of a lobar artery, with the second lobar artery embolized after a 2-week interval. Embolization is performed via a percutaneously placed catheter by infusing 200–400 mg of polyvinyl alcohol (PVA) foam particles to achieve stasis (2). HAE, however, causes severe perioperative pain that is conventionally managed with high doses of intravenous narcotics. Potential complications of intravenous narcotics include respiratory depression and hypotension, which requires careful monitoring of the patient. Further, inadequate analgesia compromises patient compliance and may result in a less than optimum procedure.

The celiac plexus consists of ganglia and interconnecting fibers derived from the greater, lesser, and least splanchnic nerves, some of which carry nociceptive or pain impulses from the liver and other abdominal viscera. A celiac plexus block should provide excellent analgesia for both the hepatic arterial embolization procedure and recovery period. This study was undertaken to compare the perioperative analgesia achieved with a celiac plexus block to a conventional regimen of intravenous morphine.

Methods

With institutional approval and informed consent, 10 patients were scheduled to undergo a series of hepatic arterial embolizations. A random number table was used to allocate the order of the analgesic technique, either celiac plexus block or intravenous morphine, so that each patient would serve as their own control.

Our technique for celiac plexus block is that described by Moore (3). Patients were first prehydrated with 1 L of lactated Ringer's solution. Then, with the patient in a prone position, local anesthesia was injected bilaterally along the inferior edges of the 12th ribs approximately 7–8 cm lateral to the midline and at the level of the L-1 spinous process. Under fluoroscopic guidance, 15-cm long, 22-g Chiba needles were advanced toward the midline until positioned just anterior to the cephalad portion of the first lumbar body. Correct needle placement was confirmed by fluoroscopy in two planes. After a 3-mL test dose containing 1:200,000 epinephrine, the area of the celiac plexus was infiltrated on each side with 25 mL of 0.25% bupivacaine. The patient was then turned supine for the hepatic arterial embolization with continuous monitoring with use of an electrocardiograph, an automatic blood pressure cuff, and a pulse oximeter. The patient was informed that supplemental intravenous morphine was available if needed.

Pain was assessed by the patient using a 0 to 10 verbal analog scale, 0 being "no pain" and 10 being "extreme pain." The evaluations were collected immediately after the procedure, then at 8 and 24 hr after the procedure. The intravenous morphine administered for the procedure and recovery period were also recorded at these time points.

Statistical analysis was performed with use of Wilcoxan matched-pairs rank-sum test with statistical significance assigned at $P < 0.05$ (4). Values are reported as the mean $\pm$ SD.

Results

The protocol to randomize the order of analgesic technique was terminated when patients, whose first

Table 1. Celiac Plexus Block (CPB) Compared with Intravenous Morphine (IVMS)

	Embolization (Emb)		0–8 hr After Emb		8–24 hr After Emb	
	MS (mg)	Pain Score	MS (mg)	Pain Score	MS (mg)	Pain
IVMS	8 ± 5	8 ± 2	36 ± 12	9 ± 1	39 ± 18	6 ± 2
CPB	0*	0*	0*	0*	4 ± 2*	1 ± 1*

*P < 0.05.

HAE was performed in conjunction with a celiac plexus block, reported inadequate analgesia with intravenous morphine and requested to be withdrawn from the study. Five patients completed the study, receiving intravenous morphine for the first HAE and a celiac plexus block for the second embolization. After a celiac plexus block, patients reported less pain and required less narcotic medication at all time points (Table 1). Of note, patients stated that they preferred avoiding the sedation associated with intravenous morphine. No complications were associated with celiac plexus block. To the extent that there was no detectable difference in the required volume of embolizing material, the vasodilation associated with celiac plexus block does not appear to affect the HAE procedure.

Discussion

Hepatic arterial embolization is used for the palliation of hepatomegally and severe pain in patients with unresectable hepatic tumors (1,2). Infusion of the PVA foam particles, however, is associated with a "searing" pain in the right upper quadrant. Patients then experience a deep visceral pain, presumably due to the swelling of the liver within its capsule. Visceral pain is poorly controlled with intravenously administered narcotics (5), and the patient's discomfort may be compounded by narcotic-associated side effects such as nausea, pruritis, paralytic ileus, and urinary retention.

This study demonstrates that, compared with intravenous morphine, a celiac plexus block achieves more satisfactory pain relief for patients undergoing hepatic arterial embolization. The need to terminate the study is consistent with our previous experience in managing HAE patients with intravenous morphine: of 19 patients who underwent 42 HAEs, all patients complained of severe pain after each of the procedures. Further, after a celiac plexus block, patients are more alert, require less monitoring, and are able to resume a normal dietary intake more rapidly than when intravenous morphine is used for analgesia. Since instituting the routine use of celiac plexus blocks, we have managed 14 patients who have undergone 31 HAEs with similar success. Overall, compared with patients managed with intravenous morphine, patients managed with a celiac plexus block are generally discharged from hospital 1 day sooner.

The placement of a celiac plexus block under fluoroscopic guidance is straightforward and usually does not require more than 15 min. Hypotension may be avoided by prehydrating the patient (6). Reported complications include insertion of the needle into the peritoneum and possible organ puncture, inadvertent subarachnoid injection, and systemic toxic reaction to the local anesthetic (3). Computed tomography (CT)-guided needle placement for celiac plexus block has been advocated as safer than using fluoroscopy or bony landmarks for guidance (7,8). Although CT-guidance is appropriate for patients undergoing a permanent lytic block, we have found fluoroscopic guidance far more conservative of time and cost.

In conclusion, we have extended use of celiac plexus blocks to patients undergoing hepatic arterial embolization, achieving profound analgesia and reduction in narcotic requirement. We recommend celiac plexus block for analgesic management of patients undergoing hepatic arterial embolization.

References

1. Chuang VP, Wallace S. Hepatic artery embolization in the treatment of hepatic neoplasms. Radiology 1981;140:51-8.
2. Chuang VP, Soo CS, Wallace S. Ivalon embolization in abdominal neoplasms. AJR 1981;136:729-33.
3. Moore DC. Regional Block: A handbook for use in the clinical practice of medicine and surgery. Springfield: Thomas 1965: 145-62.
4. Hollander, Myles, Wolfe. Nonparametric Statistical Methods. New York: John Wiley & Sons, 1973:67-75.
5. Procacci P, Zoppi M. Pathophysiology and clinical aspects of visceral and referred pain. In: Bonica J, ed. Advances in Pain Research and Therapy. New York: Raven Press, 1983;5:643-56.
6. Hupert C, Zeig N, Sieglen-Fortunato L, Ciolino RC. Celiac plexus blocks provide pain relief for malignant and benign visceral pain. N Engl J Med 1987;84:573-6.
7. Haaga JR, Kori SH, Eastwood DW, Borokowski GP. Improved technique for CT-guided celiac ganglia block. AJR 1984; 142:1201-4.
8. Filshie J, Golding S, Robbie DS, Husband JE. Unilateral computerised tomography guided cceliac plexus block: a technique for pain relief. Anaesthesia 1983;38:498-503.

Interpleural Bupivacaine for Postoperative Pain during Lactation

Paul A. Baker, MB, ChB FFARACS and David Schroeder, MB, ChB FRACS

The distribution of bupivacaine has not been previously described with regard to human lactation and breast-fed infants. We present data from a patient who while breast-feeding received a bupivacaine infusion through an interpleural catheter for 5 days.

Case Report

A 33-year-old woman weighing 78 kg with known cholelithiasis in pregnancy presented 10 months postpartum with further severe bouts of biliary colic, eventually requiring hospital admission for control of pain. At this time, she was breast-feeding her 9.35 kg infant 4 times a day. She expressed a strong desire to continue breast-feeding in the immediate postoperative period. It was decided that postoperative analgesia could be most appropriately provided by continuous interpleural bupivacaine (1). The study was undertaken because little is known about the distribution of bupivacaine in this setting. Research Ethics Committee approval was gained and written informed consent obtained from the patient to use continuous interpleural analgesia and measure bupivacaine levels in maternal blood, breast milk, and infant blood.

Methods

Before premedication, breast milk was expressed and

used for feeding in the immediate postoperative period. After anesthetic induction with propofol 150 mg, radial artery cannulation for blood sampling was performed, and an interpleural catheter inserted in the 7th right interspace 10 cm from the spinous processes. A bolus dose of 20 mL of 0.25% bupivacaine was given via the interpleural catheter 10 min before commencing surgery to provide intraoperative analgesia and minimize anesthetic requirements. This was followed by the continuous interpleural infusion at 10 mL/hr of 0.25% bupivacaine, commencing 1 hr after the initial dose, via an IVAC™ 560 variable pressure volumetric pump (IVAC Corporation, San Diego, CA). Anesthesia was maintained with isoflurane 1%, oxygen, and nitrous oxide 66%.

Cholecystectomy and exploration of the common bile duct for multiple common duct stones were performed through a transverse incision; operating time was 135 min. Fentanyl 150 μg was given intraoperatively. Postoperatively papaveretum was available on request. No opiates were required until the 4th day when the interpleural bupivacaine infusion was discontinued for a 4-hr period. A 10-mg dose of papaveretum resulted in nausea and vomiting, so the bupivacaine infusion was recommenced. The interpleural catheter was removed at the end of the 5th day when non-opiate oral analgesics became adequate. In the postoperative period, 100-mm linear analogue pain scoring, maximal expiratory flow rate during a forced expiration measured with a Wright® Peak Flow mini-meter, and dermatome mapping of the extent of sensory denervation with ethyl chloride were used to confirm the adequacy of analgesia.

Maternal blood sampling was arterial for the first nine samples and venous, from the antecubital fossa, for the remaining four samples. These samples were taken at the following times after the bolus dose of bupivacaine: 0, 10, 20, 30 min and at 1, 2, 3.5, 6, 12, 24, 48, 72, and 106 hr. The infant's blood sample was also venous and was taken 5 hr after the morning breast-feeding and 52 hr 25 min after the bolus dose of bupivacaine. Breast-feeding recommenced 22 hr after the start of the interpleural infusion. Breast milk

Figure 1. Bupivacaine levels in maternal whole blood, breast milk, and infant whole blood over the duration of the study. Inset is an expanded view of the shaded area of the main graph over the immediate perioperative period.
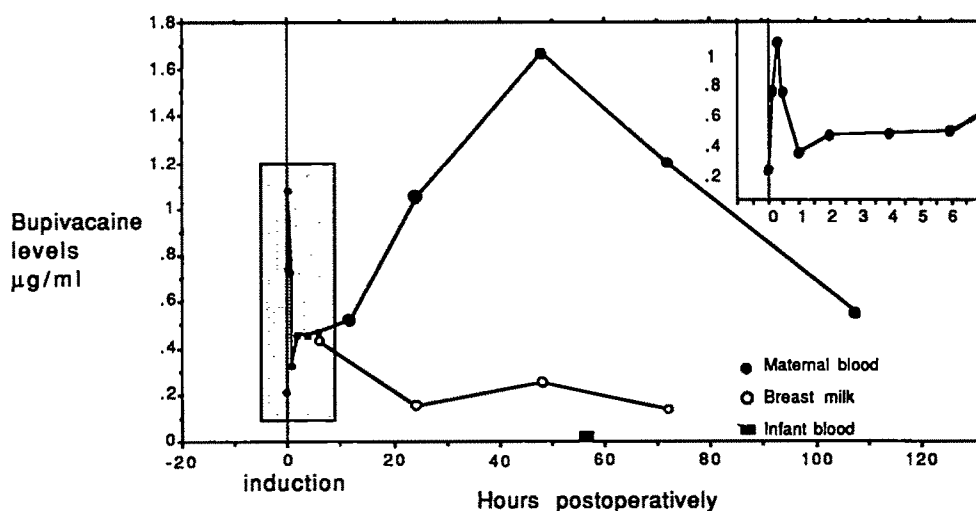
Figure 2. Maximal expiratory flow rate during a forced expiration (Peak flow) (dL/min), and pain scores (measured on a 100-mm linear analogue scale by the patient) over the study period.
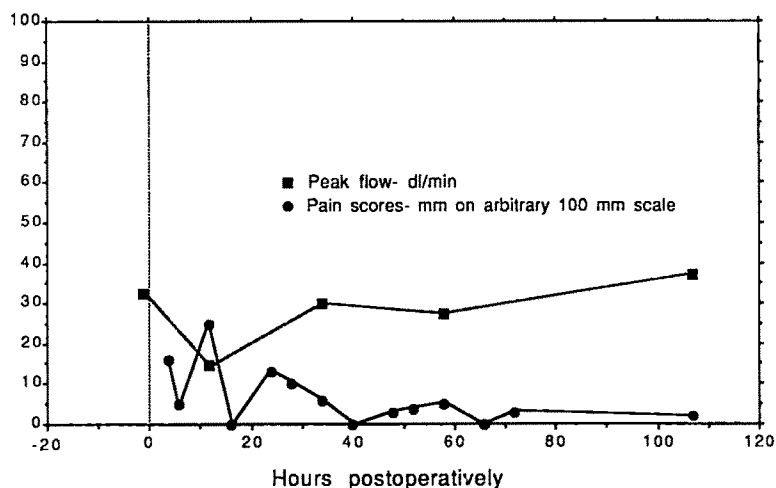
samples were taken at 6, 24, 48, and 72 hr after the bolus dose of bupivacaine.

Whole blood bupivacaine levels were determined by gas chromatography, with NaOH (100 μL 0.5N) and toluene (200 μL) added, with use of cyproheptadine as an internal standard (2). Breast milk levels of bupivacaine were assayed using a modified method of Mather and Tucker (3) incorporating gas-liquid chromatography with nitrogen selective detection.

Results

Bupivacaine concentrations are expressed graphically in Figure 1. The peak level of 1.67 μg/mL in maternal blood was reached at 47 hr after commencement of the bupivacaine infusion, and levels then declined—possibly due to improved metabolism and elimination, secondary to increasing maternal activity. The infant's blood sample was taken 5 hr after the peak

maternal blood level. Bupivacaine levels were undetectable in the infant's blood. Breast milk levels were maximal immediately postoperatively.

Pain scores shown in Figure 2 confirm the adequacy of analgesia. Maximal expiratory flow rates during a forced expiration (peak flows) returned to baseline levels within 34 hr. Sensory loss to ethyl chloride spray extended from T-4 to T-10 on the right for the duration of the bupivacaine infusion. Despite numbness of the right nipple, breast-feeding continued normally from the first postoperative day. Infant neurobehavioral testing was not conducted, but no unusual infant behavior was noted by us or the mother throughout the study.

Discussion

Cholelithiasis requiring surgery postnatally is not uncommon (4), and the more conventional use of

opiate analgesics can produce problems for the breast-feeding mother, including nausea and vomiting, sedation, fluctuating levels of analgesia, and possible drug effects on the infant. Interpleural infusion of bupivacaine is an effective alternative form of analgesia after cholecystectomy (1), and a continuous infusion technique has been described (5) and was adopted for our patient. Our dose of 0.13 $mL\cdot kg^{-1}\cdot hr^{-1}$ of 0.25% bupivacaine is considerably less than a maximal infusion rate of 0.5 $mL\cdot kg^{-1}\cdot hr^{-1}$ of 0.25% bupivacaine with 1:200,000 epinephrine used safely and effectively after thoracotomy in children (6).

The value of breast-feeding has been well established, particularly for newborn or premature infants (7). This generally justifies continuing breast-feeding in the presence of maternal medication, unless the drug is harmful to the infant. Extensive studies (8) of the effect of bupivacaine on neonates through placental transfer prove that therapeutic maternal use is safe for the neonate. One report (9) demonstrated no detectable bupivacaine in breast milk after the termination of epidural anesthesia used in labor. Bupivacaine by continuous infusion, however, presents a constant maternal blood level of the drug for distribution into milk. Bupivacaine levels in neonates in this context have not been previously studied.

Arterial rather than venous blood concentrations may more closely reflect levels of drug in well perfused vital organs, particularly during the first 60 min after an injection of local anesthetic (10). Arterial sampling was chosen for this reason, but the arterial cannula was removed for patient comfort after 12 hr.

Bupivacaine is a weak base and is lipid soluble (11). These characteristics would theoretically favor drug transfer into breast milk (12). With use of the highest concentration of bupivacaine in breast milk seen in our patient and assuming the standard milk ingestion of 150 $mL\cdot kg^{-1}\cdot day^{-1}$, the infant received at most 0.614 mg/day of bupivacaine. This corresponds to 0.1% of the maternal dose, which was 600 mg/day. This compares favorably with the distribution of morphine, which has a 0.4% ratio of infant to maternal dose. Morphine is concentrated and maintained in breast milk (13) and, therefore, it is possible with repeated doses or infusions of maternal opiates that the infant could be exposed to relatively high doses.

Blood concentrations of bupivacaine in breast-fed infants depends on a number of factors including the age and maturity of the infant, the dose of bupivacaine in the milk, the oral bioavailability of bupivacaine, and its rate of clearance in the infant. The single blood sample from this infant with no bupivacaine confirms negligible, if any, infant exposure to bupivacaine from breast milk.

The present case report suggests that interpleural analgesia by infusion of bupivacaine offers comfortable conditions for the breast-feeding mother after cholecystectomy and is apparently safe for the infant.

References

1. Reiestad F, Strömskag KE. Interpleural catheter in the management of postoperative pain. A preliminary report. Reg Anesth 1986;11:89–91.

2. Nancarrow C, Runciman WB, Mather LE, Upton RN, Plummer JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and the brain of the sheep. Anesth Analg 1987;66:925–35.

3. Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. J Pharm Sci 1974;63:306–7.

4. Bouchier IAD. Gallstones: formation and epidemiology. In: Blumgart LH, ed. Surgery of the Liver and Biliary Tract. London: Churchill Livingstone, 1988:510.

5. Rosenberg PH, Scheinin BMA, Lepäntolol MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 1987;67:811–3.

6. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988; 69:261–4.

7. Oseid B. Breast feeding and infant health. Sem Perinatol 1979;3:249–53.

8. Kileff ME, James FM, Dewan DM, Floyd HM. Neonatal neurobehavior responses after epidural anesthesia for cesarean section using lidocaine and bupivacaine. Anesth Analg 1984; 63:413–7.

9. Naulty JS, Ostheimer G, Datta S, Weiss JB. Bupivacaine in breast milk following epidural anesthesia for vaginal delivery. Reg Anesth 1983;8:44–5.

10. Tucker GT, Mather LE. Pharmacokinetics of local anaesthetic agents. Br J Anaesth 1975;47:213–24.

11. Cousins MJ, Mather LE. Clinical pharmacology of local anaesthetics. Anaesth Intensive Care 1980;8:257–77.

12. Atkinson HC, Begg GJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1988;14:217–40.

13. Findlay JWA, De Angeli RL, Kearney MF, Welch RM, Findlay JM. Analgesic drugs in breast milk and plasma. Clin Pharmacol Ther 1981;29:625–33.

Successful Resuscitation of Bupivacaine-Induced Cardiac Arrest Using Cardiopulmonary Bypass

William B. Long, MD, FACS, Stuart Rosenblum, MD, PhD, and Ian P. Grady, MD

Key Words: ANESTHESIA, LOCAL—bupivacaine.

Cardiotoxic responses to local anesthetic agents have been reported as a cause of death in patients undergoing operative procedures, despite close patient monitoring, the presence of personnel fully trained in advanced cardiac life support, and the ready availability of resuscitative drugs and equipment. In this report we present a case of bupivacaine-induced cardiac arrest that after failure of resuscitation by medical means, was successfully treated by the rapid initiation of cardiopulmonary bypass.

Case Report

A 27-year-old previously healthy white female mill worker was cleaning a veneer machine when a roller caught her right hand and drew it into the machine. She suffered a severe degloving injury to the second, third, fourth, and fifth digits with open fracture of the distal interphalangeal joints, and devascularization of each affected digit. A superficial laceration was present on the extensor surface of the right hand, with no evidence of an extensor tendon injury. At a local hospital she was given 2 g intravenous cefazolin, 0.3 mg buprenorphine, and a diphtheria/tetanus toxoid booster, and was transferred to our hospital by air ambulance. Six mg of morphine sulfate was given intravenously during the 45-min flight. Upon arrival the patient was taken directly to the operating room for debridement, Kirschner wire fracture stabilization, and microvascular arterial repair. Preoperative laboratory studies revealed normal values for serum electrolytes, blood urea nitrogen, and creatinine. He-

mogram was normal except for a white cell count of $15.7 \times 10^3/mm^3$ ($10^{12}/L$). Preoperative chest radiographs and electrocardiographs were not obtained.

The operation began 5 hr after injury. Electrocardiographic, pulse oximeter, and automatic blood pressure monitors were used. The patient was given 2 g cefazolin plus 0.625 mg droperidol and 5 mg midazolam for intravenous sedation. Using a transaxillary technique, the anesthesiologist gave a test dose of 75 mg 1.5% lidocaine with epinephrine (5 mL) followed by 450 mg of 1.5% lidocaine with epinephrine (30 mL). A satisfactory axillary block was obtained for 90 min, at which time a repeat block was performed, this time using 75 mg of 0.25% bupivacaine with epinephrine (30 mL). Just before bupivacaine injection, aspiration was without return of blood. Within 3 min of injection the patient had a global tonic-clonic seizure followed rapidly by ventricular fibrillation. The patient had no spontaneous respirations nor palpable carotid pulses.

Cardiopulmonary resuscitation was begun immediately with 100% oxygen by bag-valve-mask and closed chest cardiac compressions. Palpable femoral pulses were present during chest compressions. Tracheal intubation and mechanical ventilation were substituted for bag-valve-mask ventilation. An attempt at defibrillation with 300 J failed. Epinephrine 1 mg (1 mL of 1:1000) followed by 50 mEq of sodium bicarbonate were administered intravenously, and electrical defibrillation was again unsuccessful. Bretylium, 300 mg, was administered intravenously, and again electrical defibrillation was unsuccessful. Sodium bicarbonate, 100 mEq, and calcium chloride, 1 g, were administered intravenously. Two more attempts at defibrillation were unsuccessful. An arterial blood gas sample showed a pH of 7.8, Pco_2 of 19.5 torr (2.6 kPa), Po_2 of 284 torr (37.9 kPa), and an HCO_3^- of 32.8 mEq/L. Serum electrolyte levels and blood chemistries were normal except for a potassium of 2.4 mEq/L. Following adjustment of the ventilatory rate, a repeat measurement showed serum potassium to be 5.2 mEq/L. Her hematocrit was 27.8%. Five

hundred mg of methylprednisolone was administered intravenously in an attempt to minimize any possible ischemic brain damage.

By this time, 1 hr, 40 min had elapsed since the onset of ventricular fibrillation. We decided to try resuscitating the patient with cardiopulmonary bypass in an effort to improve coronary artery perfusion and convert the patient's EKG rhythm to normal sinus. Heparin, 7500 units, was given intravenously through a right subclavian venous catheter. A 16 F arterial cannula and a medium-sized venous cannula were placed in the right femoral artery and vein. On partial bypass the maximal flow rate was only 2.5 L/min (1.2 L/min/m^2). To obtain greater flow the chest was opened via a median sternotomy incision, and the patient was placed on full cardiopulmonary bypass, using a two-stage venous catheter in the right atrium, and the previously placed 16 F femoral arterial catheter. With this technique, flow increased to 4.5 L/min (2.4 L/min/m^2), while the mean blood pressure ranged between 40 and 50 mm Hg (5.3–6.7 kPa).

Arterial blood gas analysis during bypass revealed a pH of 7.55, Pco$_2$ of 28.7 torr (3.8 kPa), Po$_2$ of 352 torr (46.9 kPa). Her hematocrit was 13.2%, and she had a prothrombin time of 13.1 sec, partial thromboplastin time of 50.4 sec, a plasma fibrinogen level of 76 mg/dL (0.76 g/L), and a platelet count of 144 × 10^3/mm^3 (10^{12}/L). Four units of packed red blood cells, 4 units of fresh frozen plasma, and 2 units of platelets were given. Repeat hematocrit after transfusion was 23.7%. The patient was cooled to 32°C. Temporary pacing leads were placed on the right atrium and left ventricle. Direct DC cardioversion with 20 J, followed immediately by A-V sequential pacing, converted her ventricular fibrillation to a narrow QRS complex paced rhythm at 92 min^{-1}. The patient was then rewarmed to 37°C. Despite a paced A-V rhythm, mean arterial pressure remained in the range of 40 to 50 mm Hg (5.3–6.7 kPa) as bypass flow rates were decreased. Infusions of a volume expander and phenylephrine failed to increase mean arterial blood pressure above 60 mm Hg (8 kPa). Calcium chloride, 500 mg, was then given intravenously. The mean arterial pressure increased to the range of 80 to 90 mm Hg (10.7–12 kPa), and cardiopulmonary bypass was successfully terminated 2 hr 45 min after onset of ventricular fibrillation. Total bypass time was 1 hr 30 min.

Following protamine to antagonize the circulating heparin, the right subclavian central venous catheter was replaced with a pulmonary arterial catheter for postoperative monitoring. Her cardiac index off bypass was 3.52 L/min/m^2, with a systolic blood pressure of 100 mm Hg (13.3 kPa). The reconstructive hand procedure was cancelled. Purposeful movement in all four limbs was observed when the anesthetic was discontinued. With temporary pacing and ventilatory assistance, the patient was transferred to the intensive care unit.

Postoperatively the patient did well. Within 1 hr, she had a normal sinus rhythm and pacing was discontinued. The tracheal tube and the pacing leads were removed the following day. The patient remained in normal sinus rhythm throughout the remainder of her hospital course. Serial CPK isoenzymes showed no evidence of myocardial damage. The only neurological symptom was a mild left lateral leg dysesthesia. The patient subsequently returned to the operating room four times for repair of her hand injuries, which eventually required amputation of two digits at the proximal inter-phalangeal joint, and three skin grafting procedures. One year postoperatively the patient is doing well undergoing rehabilitative therapy for her hand injury. She has not yet returned to work.

Discussion

Bupivacaine-induced toxic reactions resulting in cardiovascular collapse are rare but carry a high mortality rate. In the 1978 series of Moore et al. of 11,080 major nerve blocks with bupivacaine, 15 systemic reactions occurred (0.14%), 13 as a result of inadvertent intravascular injection, and two as a result of rapid absorption from the injection site (1). All 15 patients had symptoms of central nervous system toxicity and recovered without sequela.

Sudden cardiac arrest following clinical doses of etidocaine and bupivacaine was brought to the attention of the medical community in 1979 by Albright's report of six cases of cardiac arrest following major nerve block (2). Some of these cases were characterized by prolonged and difficult resuscitation (2). As bupivacaine became more widely used, reports of cardiac toxicity increased. In October 1983 Albright reported to the Food and Drug Administration's Anesthetic Life Support Advisory committee 49 cases, occurring over the preceding 10 years, of cardiac arrest or arrhythmias severe enough to require cardioversion after administration of bupivacaine (3). Of these cases, 27 involved the use of 0.75% bupivacaine in obstetrical patients in a dosage range of 50–180 mg. There were 10 deaths in this group. Six out of eight patients who received 0.5% bupivacaine in a dose of 75–135 mg died. There were 14 nonobstetric patients, five of whom died, with

doses in the range of 50–360 mg. The overall mortality was 21/49 (43%) (3). Partially as a result of these case reports, the 0.75% bupivacaine formulation is no longer recommended for obstetrical use (3).

The mechanism of bupivacaine cardiotoxicity has been ascribed to decreases in cardiac contractility and in the maximum speed of depolarization of the action potential produced by binding of bupivacaine to sodium channel receptors with resultant blocking of sodium channels in nerve membranes. In the heart this predisposes to reentrant conduction pathways, leading to ventricular arrhythmias (4). Binding of amide local anesthetics, which are weak bases, to myocardial sodium channel receptors is enhanced by acidosis and tachycardia (4,5). Unfortunately, acidosis and tachycardia occur frequently during cardiac arrest, causing even greater binding of local anesthetics to sodium channel receptors. This may account for the prolonged cardiac arrest, despite appropriate therapy, sometimes seen in bupivacaine-induced cardiac arrest. Therapy for bupivacaine toxicity should be directed toward dissociating bupivacaine from the myocardial sodium channel.

The use of cardiopulmonary bypass as a treatment for local anesthetic induced cardiac arrest has been previously discussed in the literature. Freedman et al., for example, gave 16 dogs 30 mg/kg of intravenous lidocaine, a dose sufficient to cause cardiac arrest in each animal (6). The dogs were separated into two groups of eight for treatment. One group was treated with antiarrythmic drugs, pressor drugs, and defibrillation as appropriate. All but two were dead within 30 min. The other group of animals was treated for 90 min with cardiopulmonary bypass and intravenous norepinephrine for circulatory support followed by electrical defibrillation. There were no fatalities in the second group. Lidocaine clearances measured while dogs in the second group were on bypass were equal to clearances in a third group of eight dogs, not on cardiopulmonary bypass, given nonlethal lidocaine doses of 3 mg/kg. The authors suggested that cardiopulmonary bypass could be an effective therapy for massive local anesthetic overdose (6).

Noble et al. reported in 1984 an inadvertent intravenous overdose of lidocaine (2 g) in a patient in whom cardiopulmonary bypass was being terminated after cardiac surgery. Asystole developed and cardiopulmonary bypass was immediately reinstituted. After 45 min of further bypass, atrial pacing established an effective paced rhythm. With this rhythm, weaning from bypass was successful. Spontaneous normal sinus rhythm was restored within 4 hr, and the patient suffered no sequela (7).

Cardiopulmonary bypass provides circulatory support far superior to closed chest cardiac massage. The improved tissue perfusion minimizes metabolic acidosis, which in turn decreases binding of local anesthetics to myocardial sodium channel receptors. Cardiopulmonary bypass also maintains hepatic blood flow, which is necessary for the liver to detoxify circulating local anesthetic agents (8).

Cardiopulmonary bypass may decrease bupivacaine binding to the myocardial sodium channel receptors by reversing the pathologic inability to redistribute bolus local anesthetic doses in cardiac arrest described by Freedman et al. (6,7). Once cardiac output is restored with cardiopulmonary bypass, drug redistribution occurs very rapidly (6). This may represent the major therapeutic effect of cardiopulmonary bypass in reversing local-anesthetic-induced cardiac arrest.

Two problems arose with cardiopulmonary bypass resuscitation in our patient. One was low flow rates through the femoral arterial and venous cannulas. This may have been a technical problem, and cannulation of the superior vena cava through a median sternotomy might have been avoidable. The second problem was persistent low mean arterial blood pressures following successful cardioversion. Volume infusions and phenylephrine failed to increase mean arterial pressure during attempts to wean from bypass. This may have represented decreased systemic vascular resistance from local anesthetic cardiotoxicity. An infusion of calcium chloride brought mean arterial pressures to normal levels and allowed successful discontinuation of cardiopulmonary bypass. This response to calcium chloride should generate further research in amide anesthetic toxicity reversal.

To our knowledge, this is the first case of bupivacaine-induced cardiotoxicity treated with cardiopulmonary bypass. Also, the time from arrest to successful resuscitation, 2 hr 45 min, is one of the longest yet reported. This success, we feel, is directly attributable to initiation of cardiopulmonary bypass. It is our opinion that cardiopulmonary bypass, with appropriate antiarrhythmic therapies, should become the treatment of choice in cases of local-anesthetic induced-cardiac arrest not quickly reversed by ACLS protocol. As demonstrated by this case report, resuscitation, without sequela, is possible after prolonged cardiac arrest, through the use of cardiopulmonary bypass.

References

1. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: a review of 11,080 cases. Anesth Analg 1978;57:42–53.

2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (editorial). Anesthesiology 1979; 51:285–7.

3. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986;58:736–46.

4. Cardiotoxicity of local anaesthetic drugs (editorial). Lancet 1986; 22:1192–4.

5. Kendig JJ. Clinical implications of the modulated receptor hypothesis: local anesthetics and the heart (editorial). Anesthesiology 1985;62:382–4.

6. Freedman MD, Gal J, Freed CR. Extracorporeal pump assis-

tance—novel treatment for acute lidocaine poisoning. Eur J Clin Pharmacol 1982;22:129–35.

7. Noble J, Kennedy DJ, Latimer RD, et al. Massive lignocaine overdose during cardiopulmonary bypass: successful treatment with cardiac pacing. Br J Anaesth 1984;56:1439–41.

8. Stenson RE, Constantino RT, Harrison DC. Interrelationships of hepatic blood flow, cardiac output, and blood levels of lidocaine in man. Circulation 1971;43:205–11.

9. Lippert H, Lehmann HP. S.I. Units in Medicine. Baltimore-Munich: Urban and Schwarzenberg, 1978.

Letters to the Editor

AIDS Infection Protection— Reinforced Gloves

Key Words: EQUIPMENT, GLOVES.
INFECTION, AVOIDANCE.

To the Editor:

Concern among health professionals about protection from infection has increased in the past 3 years because of the AIDS epidemic. Prophylactic maneuvers to prevent blood and secretions from infecting personnel have been recommended by the Centers for Disease Control and others that include not recapping needles, and wearing gloves, masks, and goggles (1-3). Some anesthesiologists have been reluctant to use gloves because 1) they have developed the habit of not working with gloves, 2) they believe they are less capable of performing fine motor work with gloves on, and 3) when tape is being applied, the tape adheres to the gloves, rips them, and renders them useless.

We have found that with a little practice fine motor work can be performed with gloves on the hands. We have also found that the gloves can be reinforced at the distal phalanges by applying, after the gloves have been put on, cloth adhesive tape directly to the gloves (Figure 1). Rein-

Figure 1. Latex gloves with distal phalanges covered with cloth adhesive tape.

forcing the gloves at this point makes it easy to tear and apply tape without destroying the glove. Fine motor work, such as placement of radial artery catheters, can be performed with the modified gloves since the tips of the fingers remain free of tape. Since removing the tape from the gloves would tear them, the tape is left in place once it is applied.

This simple and practical suggestion is offered in the hope that it will reduce the frustration of attempting to protect ourselves from infection while caring for our patients.

Susan L. Paglia, MD
Richard M. Sommer, MD
Department of Anesthesiology
New York University Medical Center
New York, NY 10016

References

1. Centers for Disease Control. Recommendations for prevention of HIV transmission in health-care settings. MMWR 1987;36:3-18S.
2. Arden JR. Anesthetic management of the patient with AIDS. Anesthesiology 1986;64 660-1.
3. Arden JR. Managing patients with AIDS—update. Anesthesiology 1988; 68:164-5.

Thiamine for Prevention of Wernicke's Encephalopathy: A Reminder

Key Words: METABOLISM, HYPOGLYCEMIA.

To the Editor:

Naidu and Brock-Utne (1) correctly remind us of the occurrence of hypoglycemia in alcoholics and other debilitated patients with decreased hepatic glycogen stores. They point out that the diagnosis of hypoglycemia is made more difficult during anesthesia. May I remind Drs. Naidu and Brock-Utne, however, that before a glucose bolus or infusion, it is mandatory that nutritionally depleted patients, such as alcoholics, receive thiamine in order to prevent Wernicke's encephalopathy (2). During normal carbohydrate metabolism, thiamine is consumed as an enzymatic cofactor in the hexose monophosphate shunt and the Kreb's cycle. With a large or concentrated glucose bolus in the malnourished, asymptomatic patient, thiamine stores are rapidly exhausted, aerobic glycolysis is subsequently inhibited, and nervous tissue dysfunction occurs manifesting as classic symptoms of Wernicke's encephalopathy:
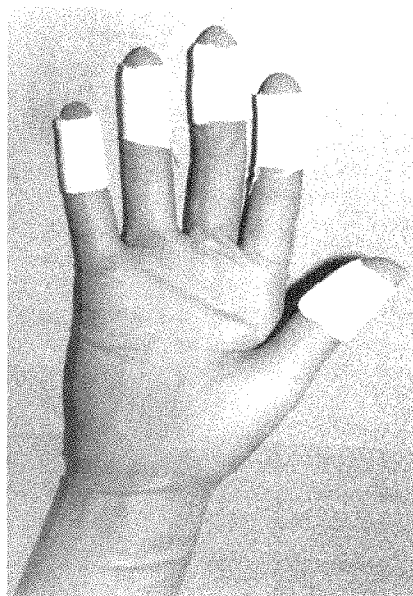
bilateral ophthalmoplegia, ataxia, and global confusion (2). Wernicke's encephalopathy is a medical emergency where delays in treatment contribute to a 10–20% mortality rate and the later development of Korsakoff's psychosis (3,4). The administration of 100 mg of parenteral thiamine to patients with established Wernicke's encephalopathy has been shown to reverse dramatically the ophthalmoplegia, global confusion, and apathy within hours (4). It is recommended that malnourished patients receive this dose of thiamine concomitantly with the institution of a glucose infusion under elective conditions or immediately after a concentrated glucose bolus in an emergency (3).

The importance of parenteral glucose solutions in the nutritionally depleted patient should not be understated. What was intraoperative hypoglycemia, however, may become a postoperative confusional state if thiamine is omitted.

Gretchen A. Mayes, MD
Department of Anesthesia
University of Arizona
Tucson, AZ 85724

References

1. Naidu R, Brock-Utne JG. Generalized convulsions following regional anesthesia: a pertinent lesson. Anesth Analg 1988;67:1192–3.
2. Watson AJS, Walker JF, Tomkin GH, Finn MMR, Keogh JAB. Acute Wernicke's encephalopathy precipitated by glucose loading. Ir J Med Sci 1981;150:301–3.
3. Reuler JB, Girard DE, Cooney TG. Wernicke's encephalopathy. N Engl J Med 1985;312:1035–9.
4. Victor M, Adams RD, Collins GH. The Wernicke-Korsakoff syndrome. Philadelphia: FA Davis, 1971:172–3.

Epidural Narcotic Use for Outpatient Pain Treatment

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—narcotics PAIN, CANCER—epidural narcotics.

To the Editor:

The findings in the recent article by Downing et al. (1) concerning outpatient epidural morphine use parallel my own experience. I would like to offer several comments of practical clinical value.

The 18-gauge polyamide epidural catheter made by Burron (Burron Medical, Inc., Bethleham, PA) is an excellent choice in view of its durability, resistance to kinking or breaking, absence of tissue reaction, and ready availability. I prefer the open-end catheter (no. EC18-0), however, instead of the bullet tip for several reasons: it is even less likely to suffer outflow obstruction, as I have seen with several bullet tip (side-port) catheters after many (hundreds) of injections; it is less likely to be associated with idiosyncratic obstruction to aspiration of cerebrospinal fluid when resting partially in the subarachnoid space, as has been reported with side-port catheters.

Tunneling the catheter subcutaneously from the back around the flank to the subcostal area with three 14-gauge,

13-cm (5¼") Angiocaths (Deseret Medical, Inc., Sandy, UT) is simple, quick, inexpensive, "nonsurgical," and provides for long-term use with routine "Hickman" catheter nursing care. The skin exit site is covered with a clear, sterile dressing, e.g., Bioclusive (Johnson & Johnson Products, Inc., New Brunswick, NJ) or Tegaderm (3M, St Paul, MN). The optimal injection cap is also a Burron product, the IN-1000 injection cap, in a distinct, bright yellow color. Using the above equipment and sterile technique, I have had no infections nor other significant complications in 27 catheter placements, the longest one being in place 13½ months. The only restriction to activity I advise is avoidance of prolonged direct contact with water at the catheter exit site, like swimming, but showering is alright.

Portable continuous infusion pumps may be in vogue, but I do not find them trouble-free or less expensive for the patient, even if insurance is supposed to cover the cost. The 20% Medicare cost share of renting one of the portable infusion pumps, plus having the pharmacist fill the reservoir with morphine, can easily run to well over $200 per month. Injecting the catheter once or twice a day with a dilute solution of commercially available morphine or hydromorphone (Dilaudid, Knoll Pharmaceuticals, Whippany, NJ) (2) is simple, effective, and inexpensive. Using multidose morphine sulfate (3) (Eli Lilly & Co., Indianapolis, IN) in 15 mg/mL, 20-mL vials, or, if preservative-free drug is desired, using Dilaudid-HP (Knoll Pharmaceuticals) in 10 mg/mL ampules, diluting either preparation to 5 mg/mL morphine equivalents, a wide range of doses with minimal volume can be injected for less than $1 per day. This low cost is genuinely appreciated by terminally ill cancer patients on a low fixed income.

Lastly, if any concern arises about location of the catheter tip, such as why there is a change in drug response, have the radiologist inject the catheter with water-soluble dye and confirm its location.

Edson O. Parker, MD
Pain Institute of Nevada
Las Vegas, Nevada 89106

References

1. Downing JE, Busch EH, Stedman PM. Epidural morphine delivered by a percutaneous epidural catheter for outpatient treatment of cancer pain. Anesth Analg 1988;67:1159–61.
2. Parker EO, Brookshire GL, Bartel SJ, et al. Effects of epinephrine on epidural fentanyl, sufentanil, and hydromorphone for postoperative analgesia (abstract). Anesthesiology 1985;63:A235.
3. Du Pen SL, Ramsey D, Chin S. Chronic epidural morphine and preservative-induced injury. Anesthesiology 1987;67:987–8.

On Hot Mice, Cold Facts, and Would-Be Replication

Key Words: ANESTHETICS, GASES—nitrous oxide. INTRAVENOUS—thiopental. HYPOXIA, CEREBRAL.

To the Editor:

We found that nitrous oxide (N_2O) reduces thiopental-induced prolongation of survival in hypoxic mice at ambi-

Hartung & Cottrell's Protocol
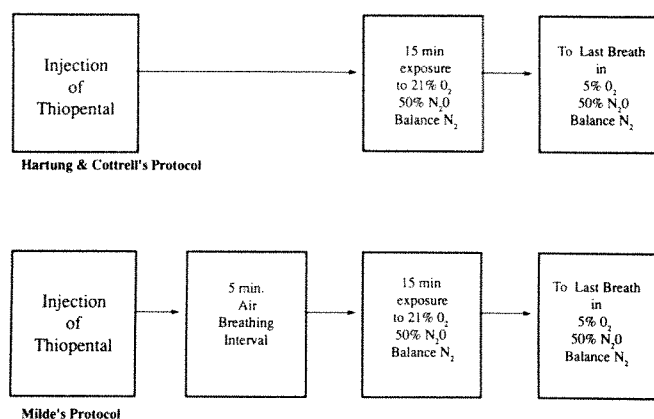
Milde's Protocol

Figure 1. Experimental protocol: difference between that of Hartung and Cottrell and that of Milde. In Milde's experiment, total elapsed time between injection of thiopental and subjection to hypoxia was increased 33% by insertion of a 5 min air-breathing interval between injection of thiopental and subjection to 15 min of a normoxic gas mixture containing 50% nitrous oxide. On repetition, this difference contributed to the observed discrepancy in results.

ent temperature (1). Milde found that N_2O does not have that effect (2). We applaud Milde's intention in repeating our experiment in order to check the reproducibility of our result. This is the stuff of science and should be done more often. However, replication requires adherence to the original experimental protocol. Critically important variables cannot be substantially altered. Specifically, we agree with Milde that "differences in the time between the intraperitoneal injection of barbiturate and the onset of hypoxia affect survival time" in the hypoxic mouse model (2).

In our experiment, mice were injected with thiopental and immediately subjected to a normoxic gas mixture containing 50% N_2O for 15 min, then subjected to an hypoxic gas mixture containing 50% N_2O until last breath. Milde followed this protocol exactly, except for the insertion of a 5-min period of air breathing between injection of thiopental and subjection to the 15 min normoxic/N_2O gas mixture (see Figure 1).

Five minutes of air breathing might be critically important here. At about 1.5 min after intraperitoneal injection of thiopental (10 mg/100 g), mice lose their righting reflex. By 3 min they lose the startle reflex (movement or blinking in response to tapping on their container). At 5 min, mice are unresponsive to painful stimuli and are as anesthetized as they will be for the next hour. The stimulatory effect of N_2O on cerebral metabolism (3–6) may be precluded in brains that are already maximally depressed. Accordingly, Milde's insertion of a 5 min air-breathing interval after thiopental injection but before N_2O exposure may have allowed brain metabolism to become so depressed before N_2O exposure that subsequent N_2O delivery had little or no stimulatory effect. A lack of stimulation would conserve cerebral metabolites and preserve the protective effect of thiopental.

In order to test this possibility we performed two new experiments, exposing two groups of thiopental-treated mice to hypoxia with N_2O: 20 mice without an intervening 5 min air-breathing interval (as in our original protocol) and

20 mice with an intervening 5 min air-breathing interval (as in Milde's study). Mice were randomly assigned to each group and each protocol was executed alternately in order to randomize nontreatment effects across groups (e.g., temperature). We hoped that the difference in protocol between these two new experiments would account for the discrepancy between our original result and Milde's result. However, N_2O had a deleterious effect in both the air-interval and no-air-interval groups. With the air interval, our mice lived 8.3 ± 0.82 min (SE), significantly less than Milde's mice (11.59 ± 1.52). Without the air interval, our mice lived 6.4 ± 0.78 min, significantly less than either Milde's or our air-interval groups. For both of our new thiopental/N_2O groups, survival time was significantly reduced compared with both Milde's and our thiopental-without-N_2O groups done at ambient temperature (11.84 ± 2.21 and 13.9 ± 2.6, respectively). In short, the 5 min air-breathing interval substantially ameliorated but did not eliminate the discrepancy between our original result and Milde's result. We have now found a negative effect of N_2O on thiopental-induced survival time during three hypoxia experiments (two reported here and one original) and one anoxia experiment (1). Milde found a negative effect of N_2O on thiopental-induced survival time in one hypoxia experiment (mice kept at 36°C) and failed to find it in another (mice at 30.4°C [2]). According to the weight of the evidence, we stand by the central point of our article that nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice (1).

With regard to the issue of thiopental's protective effect independent of N_2O, Milde found prolonged survival when thiopental treated mice were allowed to thermoregulate down to 30.4°C. She found no such effect when mice were kept at 36.1°C. This latter result contrasts with the finding of Artru and Michenfelder that pentobarbital extends survival time by nearly 300% in mice maintained at 37°C. It is possible that this difference between Milde's result and that of Artru and Michenfelder is due entirely to the difference between thiopental and pentobarbital. Nevertheless, our findings and those of many previous investigators (see references cited in our article [1]) caution against the conclusion that thiopental has no protective effect independent of hypothermia (cf. 8).

John Hartung, PhD
James E. Cottrell, MD
Department of Anesthesiology
State University of New York
Health Science Center at Brooklyn
Brooklyn, NY 11203

References

1. Hartung J, Cottrell JE. Nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice. Anesth Analg 1987;66:47–52.

2. Milde LN. The hypoxic mouse model for screening cerebral protective agents: a reexamination. Anesth Analg 1988;67:917–22.

3. Sakabe T, Tsutsui T, Maekawa T, Ishikawa T, Takeshita H. Local cerebral glucose utilization during nitrous oxide and pentobarbital anesthesia in rats. Anesthesiology 1985;63:262–6.

4. Hoffman WE, Miletich DJ, Albrecht RF. The effects of midazolam on cerebral blood flow and oxygen consumption and its interaction with nitrous oxide. Anesth Analg 1986;65:729–33.

5. Colavita RD, Pelligrino DA. Beagle puppy model of the neonatal brain: effect of nitrous oxide on cerebral blood flow and metabolism. Anesth Analg 1988;67:S36.

6. Samra SK, Deutsch G, Arens JF. Effect of nitrous oxide on global and regional cerebral blood flow in humans (abstract). Anesthesiology 1988; 69:A536.

7. Artru AA, Michenfelder JD. Influence of hypothermia or hyperthermia alone or in combination with pentobarbital or phenytoin on survival time in hypoxic mice. Anesth Analg 1981;60:867-70.

8. Artru A. Survival time during hypoxia: effects of nitrous oxide, thiopental, and hypothermia. Anesth Analg 1988;67:913-6.

In Response:

Drs. Hartung and Cottrell present another interesting difference between their study (1) and mine (2). Specifically, they exposed mice to nitrous oxide (N_2O) and hypoxia after the intraperitoneal injection of thiopental but before the mice were fully sedated, whereas in our study the mice were exposed to N_2O and hypoxia 5 min after the intraperitoneal injection of thiopental after they were already sedated. I agree with their proposed hypothesis that during that 5-min interval the brain metabolism might have become so depressed by the thiopental that the subsequent exposure might have had no stimulatory effect. This would certainly simply explain the differences between our results. When Hartung and Cottrell repeated the experiments as I had done with a 5-min interval between the intraperitoneal injection of thiopental and exposure to N_2O and hypoxia under ambient temperature conditions, they too observed prolonged survival in these animals.

That they didn't observe the same length survival times as in my study is not surprising given the number of variables affecting this hypoxic mouse model. If meticulously done, survival times of several experimental groups measured in a single laboratory may be readily compared, but comparing survival times between different laboratories may be difficult because of differences in ambient temperatures that could affect body temperature of the mice, differences in $F_{I_{O_2}}$, and differences in gas flows causing differences in equilibration times for hypoxic exposure.

It should also be emphasized that survival time in the hypoxic mouse model may be influenced not only by an anesthetic's effect on brain metabolism, be it a decrease in brain metabolism by a barbiturate or an increase in brain metabolism by N_2O, but also by an anesthetic's effect on respiratory and cardiovascular function. The fact that neither respiratory nor cardiovascular function are supported or controlled in this hypoxic mouse model is what makes it only a crude screening test for brain protection. Therefore, conclusions about the cerebral protective effect of barbiturates or the deleterious effect of N_2O should not be based solely on this hypoxic mouse model but should be made upon proof in more sophisticated cerebral protective studies where all variables are rigidly controlled.

Lastly, I would like to comment upon observed differences in the protective effects of thiopental and pentobarbital in the hypoxic mouse model. In our laboratory, prolonged survival with pentobarbital has been observed by three investigators, Steen and Michenfelder (3), Artru and Michenfelder (4), and myself. I found a significantly prolonged survival time of 9.1 ± 0.7 min (mean ± SE) in mice treated with 60 mg/kg pentobarbital and body temperatures of 36.7 ± 0.1°C, N = 16). However, of the two studies done in our laboratory with thiopental, neither found prolonged survival when body temperature was maintained (1); Steen in 1977 observed that mice treated with 55 mg/kg thiopental survived 3.8 ± 0.8 min (unpublished data). Whether these observed differences between thiopental and pentobarbital are due to differences in effect on cerebral metabolism, thermoregulation, respiration, or cardiovascular function has not been determined.

Leslie Newberg Milde, MD
Mayo Clinic
Rochester, MN 55905

References

1. Hartung J, Cottrell JE. Nitrous oxide reduces thiopental-induced prolongation of survival in hypoxic and anoxic mice. Anesth Analg 1987; 66:47-52.

2. Milde LN. The hypoxic mouse model for screening cerebral protective agents: a reexamination. Anesth Analg 1988;67:917-22.

3. Steen PA, Michenfelder JD. Barbiturate protection in tolerant and nontolerant hypoxic mice: comparison with hypothermic protection. Anesthesiology 1979;50:404-8.

4. Artru AA, Michenfelder JD. Influence of hypothermia or hyperthermia alone or in combination with pentobarbital or phenytoin on survival time in hypoxic mice. Anesth Analg 1981;60:867-70.

Tourniquet Pain during Bupivacaine and Tetracaine Spinal Anesthesia

Key Words: ANESTHESIA TECHNIQUES, SPINAL. PAIN, TOURNIQUET.

To the Editor:

I read with interest the articles by Concepcion et al. (1) and Stewart et al. (2) that attempt to elucidate the mechanisms involved in tourniquet pain during spinal anesthesia. The article by Concepcion et al. gives the incidence of tourniquet pain to be 25% with bupivacaine and 60% with tetracaine spinal anesthesia. However, information on the duration of tourniquet inflation is provided only for those patients who developed tourniquet pain. Without information on tourniquet inflation times for the rest of both groups (i.e., those who did not develop tourniquet pain), it is not possible to determine the full clinical significance of these data. If the bupivacaine group had far more patients in it with short tourniquet times, this could skew the data to show that bupivacaine has less incidence of tourniquet pain when possibly this decreased incidence might only be due to the shorter tourniquet times in that group. It would be interesting to see not only data comparing tourniquet times for all members of both groups, but also to compare the tourniquet times between groups for those patients who did not develop tourniquet pain.

James J. Gibbons, MD
Department of Anesthesiology
St. Louis University School of Medicine
St. Louis, MO 63104

References

1. Concepcion MA, Lambert DH, Welch KA, Covino BG. Tourniquet pain during spinal anesthesia: a comparison of plain solutions of tetracaine and bupivacaine. Anesth Analg 1988;67:828-32.

2. Stewart A, Lambert DH, Concepcion MA, Datta S, Flanagan H, Migliozzi R, Covino BG. Decreased incidence of tourniquet pain during spinal anesthesia with bupivacaine: a possible explanation. Anesth Analg 1988; 67:833-7.

In Response:

We agree with Dr. Gibbons' comments and are happy to provide the data he requests.

The mean (±SD) duration of tourniquet inflation was 116.6 ± 35.0 min for the 20 patients who received bupivacaine and 104.0 ± 25.8 min for the 19 patients who received tetracaine.

In the bupivacaine group, 15 patients did not experience tourniquet pain. The mean time of tourniquet inflation for these 15 patients was 108.1 ± 29.5 min. On the other hand, only seven patients given tetracaine did not experience tourniquet pain. Duration of tourniquet inflation in these seven patients was 90.4 ± 29.2 min. The duration of tourniquet inflation was somewhat longer in patients who received bupivacaine. However, this difference was not statistically significant either when comparing total number of patients or the patients who did not develop tourniquet pain.

The data, therefore, indicate that the decreased incidence of tourniquet pain observed with bupivacaine spinal anesthesia was *not* due to shorter tourniquet times in this group.

Mercedes A. Concepcion, MD
Donald H. Lambert, PhD, MD
Department of Anesthesia
Brigham and Women's Hospital
Boston, MA 02115

Figure 1. Stylet wrapped around operator's fingers.

Disposal of Epidural Catheter Stylets: Taming the Snake

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—catheters.

To the Editor:

Disposal of stylets that come in epidural catheters is not always easy. They are notorious for springing out of trash cans, and disposing of them into most needle boxes can all too often prove frustrating. We have found that, after withdrawal of stylets from the catheters, if one grasps the end of the stylet in the left hand and tightly wraps it around the outstretched first and middle fingers until approximately 5 cm remains unwrapped (Figure 1), the tail, passed twice through the loops of the stylet (Figure 2), produces a secure, tidy unit (Figure 3), which is easily disposed of by dropping onto the epidural tray or into a needle box. This maneuver is fast, and contributes materially to efficient cleanup after administration of epidural anesthesia.

Figure 2. Tail passes through loop.
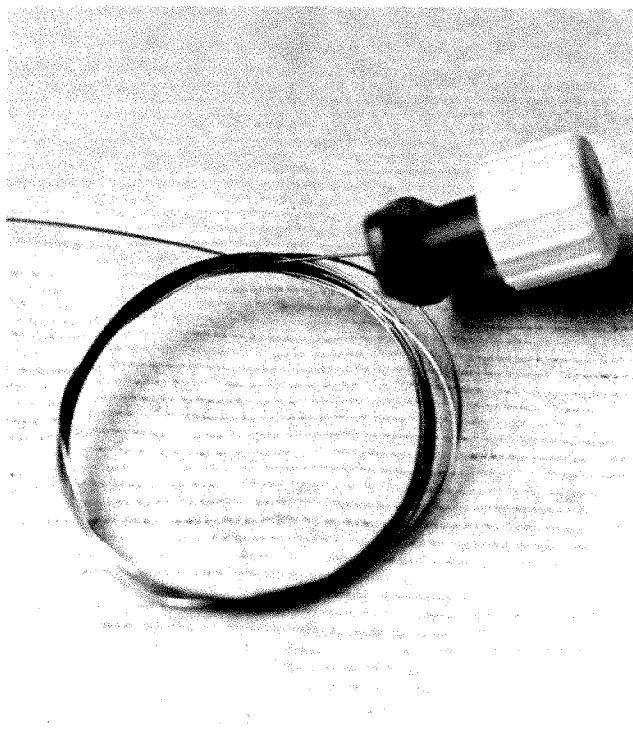
Figure 3. Unit ready for disposal.

William Camann, MD
Timothy Huckaby, MD
Department of Anesthesia
Harvard Medical School
Boston, MA 02115

Diffusion of Felt-Tip Marker Pen Ink into Intravenous Bags

Key Words: EQUIPMENT, IV INFUSION BAGS.
EQUIPMENT, MARKER INK.

To the Editor:

The use of felt-tip marking pens to label the contents of plastic intravenous solution bags is a common practice in the operating room. However, at our institution, a commonly held belief is that this practice should be avoided because of the potential diffusion of ink solvents into the fluid. A manufacturer of polyvinylchloride (PVC) intravenous bags has informed us that there is a risk of solvent permeation when using Viaflex plastic containers (Baxter Healthcare Corp., Deerfield, IL). There seems to be no proof, however, of solvent permeation, and so we decided to test whether ink solvents could diffuse through the plastic intravenous bags.

Gas chromatography was used to detect ink solvents that had diffused into a 1-L bag of normal saline (PVC bag, Baxter Healthcare) after completely covering the bag with ink from a Markette No. 590 Thinrite felt-tip marker (Eberhard Faber, Inc., Wilkes Barre, PA). Thirty minutes was allowed for diffusion of the ink into the bag. A gas chromatograph (series 750, Gow-Mac Instrument Co., Bound Brook, NJ) with a flame ionization detector was used. There was no difference between the gas chromatograph tracings of the gas bubble in the fluid bag with ink on it and a similar sample from a control bag of normal saline. However, a sample of gas from the cap headspace on the felt-tip pen revealed an abundance of several types of small molecular weight solvents. A similar abundance of solutes was found in the gas bubble after 10 μL of the ink was injected directly into the bag, thus excluding the possibility that a low gas/saline partition coefficient prevented the solutes from being detected in the gas phase. We conclude that only trivially small quantities of ink solvents could penetrate the PVC barrier, even when the entire bag was covered with ink.

Other marking pens that we have not studied may contain low molecular weight solvents with greater permeability to PVC plastics than the pens we studied. However, the failure of several types of solvents to permeate the bag in our study may suggest that PVC plastic is sufficiently impermeable to solvents so that the convenience of writing directly on the bags should not be discouraged for fear of solution contamination.

Philip E. Bickler, MD, PhD
Barbara Gold, MD
Brynte H. Johnson, MS
Department of Anesthesia
University of California
San Francisco, CA 94143

Blind Nasal Intubation by Monitoring End-Tidal CO_2

Key Words: INTUBATION, TRACHEAL—blind.

To the Editor:

Fiberoptic endotracheal intubation is generally employed for most anticipated difficult intubations. However, there still are occasions where "blind nasal intubation" can be utilized, particularly when bleeding due to trauma of any origin obscures optimal visualization. Awake blind nasal intubation is usually reserved for situations in which endoscopic intubation and ventilation of the lungs would be impossible or induction of general anesthesia before securing the airway would be hazardous.

The key to success of awake blind nasal intubation is to follow the maximal breath sounds. Therefore, the anesthetist must keep an ear close to the endotracheal tube to listen to sounds. However, when doing this, the secretion and sometimes the blood in patient's upper airway may spray/spit out of the tracheal tube with exhaled air and contaminate the anesthetist. This is particularly so while the tube is entering the glottis and an explosive cough is generally the sign of successful intubation. Contamination with patient's

blood and/or secretion is of more concern these days owing to the fear of AIDS.

Our technique to prevent this possible source of contamination is employing a capnograph or a mass spectrometer to monitor the end-tidal CO_2 ($ETco_2$) instead of listening to the breath sounds as the guide of directing and advancing the endotracheal tube during awake blind nasal intubation.

The patient is lightly sedated and topical anesthesia is administered to the nasal mucosa and nasopharynx as usual. A well-lubricated nasal endotracheal tube is gently passed through the most patent nostril into the pharynx. The opposite nostril is occluded with the mouth shut. The endotracheal tube is then connected to the breathing circuit with the sampling tube connected to a capnograph or mass spectrometer. The patient is given 100% oxygen or an anesthetic mixture, and is asked to breathe deeply. The endotracheal tube is directed and advanced with the guidance of maximal $ETco_2$ waves rather than listening to the breath sounds.

Alternatively, a FEF $ETco_2$ detector (FENEM, New York, NY) can be interposed between the tracheal tube and the anesthesia circuit. The color chart on dome of the FEF detector represents approximate ranges of $ETco_2$ from room air (0.03%, purple) to 4% (yellow). Color change of the dome assists verification of placement of tracheal tube breath by breath.

Hwa-Kou King, MD
Daniel J. Wooten, MD
Department of Anesthesiology
King/Drew Medical Center
Charles R. Drew University of Medicine and Science
Los Angeles, CA 90059

What Is MIR?

Key Words: EDUCATION, WRITING—clarity.

To the Editor:

In his review article entitled "Clinical Uses of Intravenous Anesthetic and Analgesic Infusions," White (1) introduced the abbreviation MIR to refer to a *maintenance infusion rate* for intravenous drugs used by continuous infusion. Previously, Sear and Prys-Roberts (2) used MIR to refer to the *minimum infusion rate* or the rate of drug infusion that will prevent somatic response to a painful stimulus in 50% of subjects. This is proposed as being analogous to MAC for inhaled anesthetics, the *minimal alveolar concentration* at which 50% of subjects have no somatic response to a painful stimulus, and therefore could be a method to compare anesthetic potency for intravenous drugs using this ED_{50} called MIR.

I have a problem accepting the MIR concept of Sear and Prys-Roberts because they use an analgesic end point for drugs without analgesic properties. They also confuse the matter when they talk about MIR for an intravenous hypnotic drug in the presence of nitrous oxide and various premedicant drugs.

Although authors are free to make up abbreviations and define them in their manuscripts, it would be a service to readers if authors who contribute to our journals and the editors who review their work would not allow the same abbreviations for similar but different meanings in the way that MIR was recently used by White and previously used by Sear and Prys-Roberts. This differs from the various uses of MAC because the reader can clearly differentiate *minimal alveolar concentration, monitored anesthesia care*, and what the MacDonald's Corp. sells in the way of extra big hamburgers.

Robert J. Fragen, MD
Department of Anesthesia
Northwestern Memorial Hospital
Chicago, IL 60611

References

1. White PF. Clinical uses of intravenous anesthetic and analgesic infusions. Anesth Analg 1989;68:161–71.

2. Sear JW. Pharmacokinetic and pharmacodynamic aspects of continuous infusion anaesthesia. Concept of minimum infusion rates as an index of equipotency for intravenous drugs. In: Sear JW, ed. Intravenous anaesthesiology. Clinics in anaesthesiology. London: WB Saunders, 1984:234.

Acute Left Bundle Branch Block Precipitated by Trimethaphan

Key Words: HEART, BLOCK—right bundle branch. ANESTHETIC TECHNIQUES, HYPOTENSIVE—trimethaphan.

To the Editor:

We describe a potential adverse side effect of trimethaphan administration that has not been widely recognized. A 63-yr-old man with motor attacks, hypertension treated with methyldopa, diabetes mellitus, and coronary artery disease was referred to our brain imaging laboratory for cerebral blood flow studies during rest and mild induced hypotension. The admission electrocardiogram (ECG) showed sinus bradycardia with intraventricular conduction delay and left ventricular hypertrophy with repolarization abnormality. Other diagnostic studies were unremarkable.

The patient's blood pressure on the ward had ranged from 190/100 to 120/80 mm Hg and was 190/90 mm Hg on arrival at the laboratory. The QRS complex on the monitor was similar to that obtained earlier that morning (Figure 1). After baseline cerebral blood flow studies were performed, an infusion of trimethaphan was begun at 0.2 mg/min. The patient's blood pressure decreased from 190/90 to 140/80 mm Hg and the heart rate increased from 60 to 70 beats/min after 5 min. At this time, the QRS duration appeared to have increased, as visualized on the monitor screen. The infusion was stopped and the patient carefully questioned as to the presence of anginal symptoms. He had none and appeared comfortable. Over the next several minutes, the QRS gradually returned to its baseline duration and the blood pressure returned to 190/90 mm Hg.
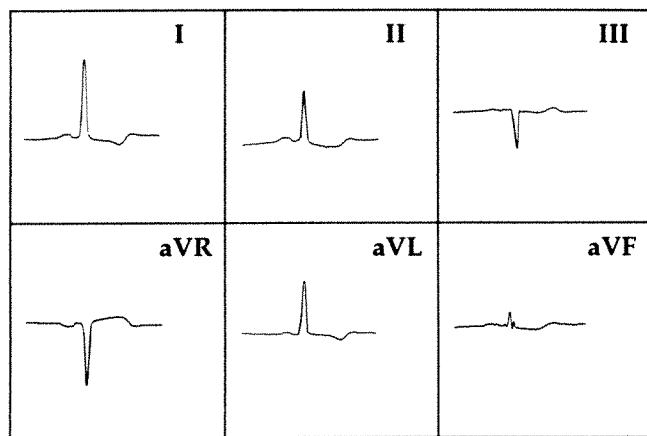
Figure 1. Electrocardiogram before procedure illustrating an intraventricular conduction delay, left ventricular hypertrophy, and repolarization abnormality.
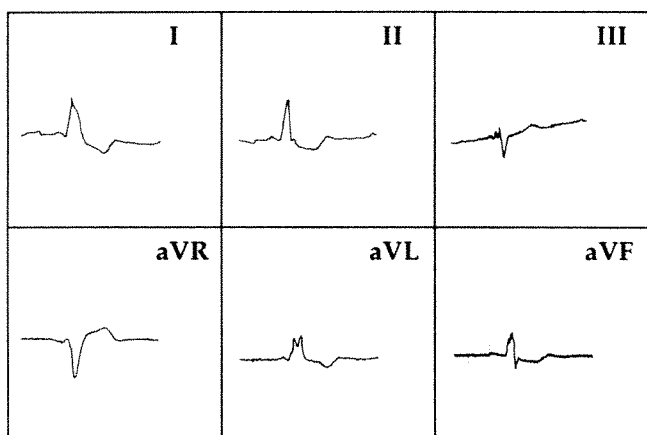
Figure 2. Limb leads recorded during trimethaphan administration showing the acute development of a left bundle branch block pattern.

The limb leads of a standard ECG machine were connected to the patient and trimethaphan infusion was restarted. After 5 min the heart rate increased to approximately 70 beats/min and the blood pressure fell from 190/90 to 140/80 mm Hg. The strip chart recording showed gradual widening of the QRS, consistent with left bundle branch block (LBBB) as shown in Figure 2. The onset of QRS widening began at exactly the same time from onset of drug infusion as the immediately previous occurrence. The drug infusion was stopped. The nadir of the blood pressure reduction during the second infusion was 115/70 mm Hg. Within 5 min of stopping the trimethaphan infusion, the blood pressure again returned to baseline level, with gradual return of the QRS to the baseline appearance as in Figure 1. The heart rate remained at 70 beats/min. Holter monitoring for 24 hr revealed sinus rhythm with occasional atrial and no ventricular premature complexes. There were three brief episodes of paroxysmal supraventricular tachycardia at a rate of 120 beats/min. During these episodes a LBBB pattern was present. A LBBB pattern also occurred

intermittently during normal sinus rhythm at rates ranging from 50 to 89 beats/min.

Based on the temporal relationship of drug infusion to the appearance of the conduction delay, unrelated to heart rate, and the lack of symptoms, we feel that trimethaphan contributed to the development of LBBB in this case. There is, to our knowledge, only one other description of LBBB associated with trimethaphan administration (1). Interestingly, that case was also associated with recent methyldopa therapy. We advise careful ECG monitoring during administration of trimethaphan in patients with evidence of intraventricular conduction delay or history of LBBB, especially with recent methyldopa therapy. Although the precipitation of LBBB by trimethaphan appears to be completely reversible, it may be confused with myocardial ischemia during induced hypotension, including the acute treatment of hypertension.

William L. Young, MD
Darren R. Gitelman, MD
Thomas K. Tatemichi, MD
Isak Prohovnik, PhD
Departments of Anesthesiology, Psychiatry, Neurology, and Radiology
Columbia University College of Physicians & Surgeons
New York, NY 10032

References

1. Di Leo M, Dalmasso M, Libero L, Bergerone S, Brusca A. Severe electrocardiographic abnormalities during arfonad administration. G Ital Cardiol 1984;14:931–4.

A Simple, Inexpensive Device to Prevent Airway Disconnection When Using Remote Capnometry

Key Words: COMPLICATIONS, DISCONNECTIONS—prevention.

To the Editor:

Accidental disconnections in anesthesia circuits are potentially extremely hazardous. Increasing regulatory and clinical emphasis on the need for monitoring components added to anesthesia circuits increases the number of friction-fit components and thus the potential for accidental disconnection. We wish to call attention to a source of disconnections in anesthesia circuits caused by the use of remote sensing capnometry and to describe a simple and inexpensive solution to the problem.

Our operating rooms are equipped with capnometers (Hewlett-Packard model 47210A) utilizing proximal airway sensors (Hewlett-Packard part no. 14360) that contain a folded infrared beam transmitter–receiver assembly. The sensor is snapped over an airway adaptor (Hewlett-Packard part no. 14361A) placed in line between the patient circuit elbow and the tracheal tube adaptor, using two disposable polypropylene 15-mm tubing couplers (Hewlett-Packard part no. 14373B). The capnometry sensor straddles the two sapphire windows built into the airway adapter, allowing

Figure 1. The Velcro strip used to form the Butler strap.
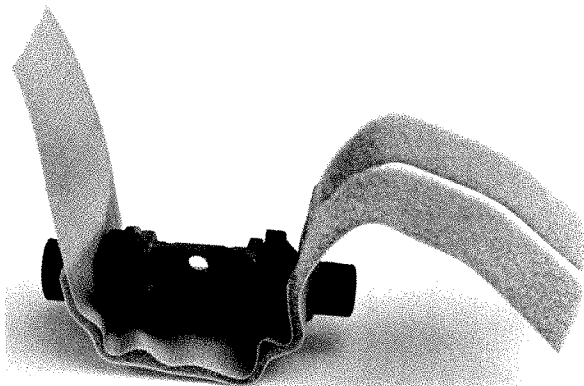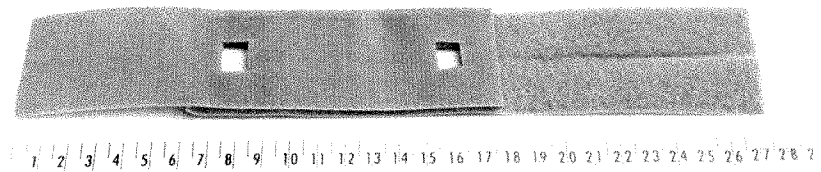
Figure 2. The airway adapter/tubing couplers are inserted through the holes in the Butler strap.

the sensor light beams to cross through gas flowing through the adaptor. The sensor contains a heater to prevent condensation.

We have encountered two problems with this configuration. First, the sensor is prone to disconnection from the airway adapter since it is held in place only by a weak friction fit between four spring-held ball bearings in the sensor module that engage four divots in the airway adapter. The spring tension on the ball bearings weakens with use. Secondly, the connection of the airway tubing couplers to the airway adapter occasionally fails to maintain a secure connection. This may in part be due to leverage on the connections produced by the weight of the rest of the patient circuit, particularly when it is not practical to support the tubing close to the sensor/adapter. A rubber

strap provided by the manufacturer was difficult to apply and remove, and only provided reinforcement for the sensor/adapter attachment without additional security for the tubing couplers.

We have devised a simple, easily duplicated, inexpensive way to prevent dissassembly of the sensor/adaptor/coupler unit, which we call the Butler strap, named for the technician responsible for its design.

The Butler Strap is made from 5-cm-wide Velcro strips (Smalley and Bates, Inc., Cedar Grove, NJ) (Figure 1). An 18-cm length of hook tape component and a 22-cm length of loop tape component are overlapped 12 cm to create a strap 28 cm in length. Holes 1.5 cm in diameter are cut 7 and 15 cm from the exposed end of the hook tape component. The exposed end of the loop tape component is cut down the center of the strap lengthwise for 10 cm, creating two tails.

Figures 2 and 3 show the assembly of the adapter/tubing coupler components using the Butler strap to secure the sensor to the airway adapter and the airway adapter to the airway tubing couplers. This system provides security and ease of use when measuring $ETco_2$ during anesthesia. It is inexpensive to make, easy to use, allows visual inspection of the airway connections, and is resistant to disassembly in the presence of water, blood, or secretions. It allows rapid disconnection in emergencies for inspection of the components.

Robert Quarnby, MD
Lester Schmitt, CRNA
Department of Anesthesiology
The Mary Imogene Bassett Hospital
Cooperstown, NY 13326

Figure 3. The capnometer sensor is placed over the airway adapter with the sensor wire passing through the split tails of the loop tape. The hook tape component is folded over top of the sensor and the tails of the loop tape component are tightly hooked to it.
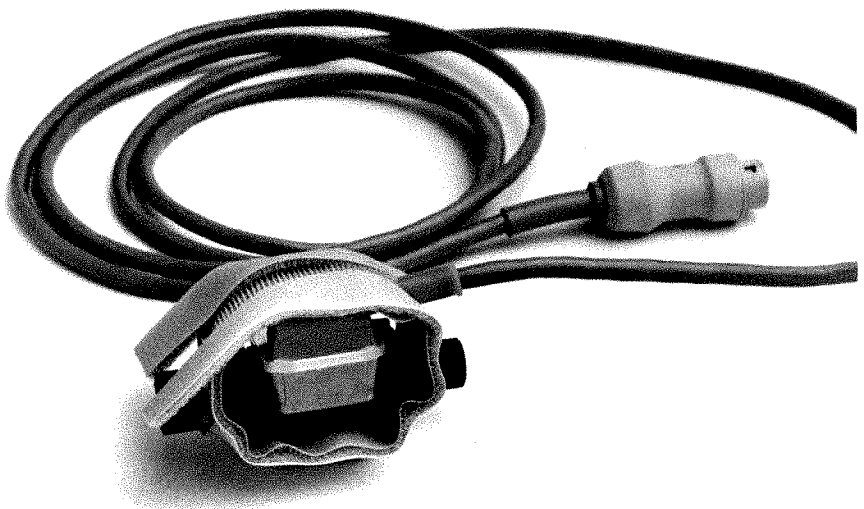
Clinical Use of Subarachnoid Neuropeptides: an Experimental Contribution

Key Words: POLYPEPTIDES, NEUROPEPTIDES—subarachnoid. ANESTHETIC TECHNIQUES, SPINAL—neuropeptides.

To the Editor:

Eisenach has pointed out the necessity of adequate animal experimental studies prior to clinical use of subarachnoid neuropeptides, including calcitonin (1). We have studied the modulation of nociceptive transmission by salmon calcitonin and other peptides for some years and think we might add some useful information to this subject. The results of our studies (2–4) add to the two references cited by Eisenach and are germane to the experimental evaluation of subachnoid salmon calcitonin.

A paper (5) referred to possible inhibition of motor coordination after intrathecal salmon calcitonin in rats, but its authors did not present experimental data to substantiate their claim that there was a slowing of the righting-reflex. We, however, could find no statistically significant effect of intrathecal calcitonin, unlike other neuropeptides, on righting-reflexes in rats (4). Furthermore, the inability of subarachnoid salmon calcitonin to create a significant modification of the tail-flick reaction (2,4; see also 5) argues against the possibility that this peptide has motor effects.

Concerning possible neurotoxicity (6), however, a clear distinction must be made between the use of the pure peptide and that of commercially available forms, due to the presence in the latter of additives or preservatives that may not be compatible with the subarachnoid route of administration. We agree with Eisenach on the importance of a precise experimental characterization before a safe and useful clinical implementation of neuropeptides can be considered. This point is particularly relevant in pain therapy (4): the reports of experimental antinociceptive activity of opioids and some nonopioid peptides have suggested to some their use with human beings (7,8), even though data on their possible adverse effects have appeared (4,9).

Sanzio Candeletti, ChD
Sergio Ferri, MD, ChD
Institute of Pharmacology
University of Bologna
Irnerio 48, 40126 Bologna
Italy

References

1. Eisenach JC. Demonstrating safety of subarachnoid calcitonin: patients or animals? Anesth Analg 1988;67:296.

2. Spampinato S, Candeletti S, Cavicchini E, Romualdi P, Speroni E, Ferri S. Antinociceptive activity of salmon calcitonin injected intrathecally in the rat. Neurosci Lett 1984;45:135–9.

3. Candeletti S, Romualdi P, Spadaro C, Spampinato S, Ferri S. Studies on the antinociceptive effect of salmon calcitonin. Peptides 1985;6(suppl. 3):273–6.

4. Spampinato S, Romualdi P, Candeletti S Cavicchini E, Ferri S. Distinguishable effects of intrathecal dynorphins, somatostatin, neurotensin and s-calcitonin on nociception and motor function in the rat. Pain 1988;35:95–104.

5. Wiesenfeld-Hallin Z, Persson A. Subarachnoid injection of salmon calcitonin does not induce analgesia in rats. Eur J Pharmacol 1984;104:375–7.

6. Shaw HL. Subarachnoid administration of calcitonin: a warning. Lancet 1982;2:390.

7. Chrubasik J, Meynadier J, Blond S, et al. Somatostatin, a potent analgesic. Lancet 1984;2:1208–9.

8. Wen HL, Mehal ZD, Ong BH, Ho WKK, Wen DYK. Intrathecal administration of beta-endorphin and dynorphin-(1–13) for the treatment of intractable pain. Life Sci 1985;37:1213–20.

9. Long JB. Spinal subarachnoid injection of somatostatin causes neurological deficits and neuronal injury. Eur J Pharmacol 1988;149:287–96.

Hazards of Henna

Key words: MEASUREMENT TECHNIQUES, PULSE OXIMETRY—henna effect.

To the Editor:

It was interesting to read the article by Cote et al. (1) about the effect of nail polish on pulse oximetry. In several areas of the Middle East it is customary to apply a solution made from crushed henna leaves (Lawsoria irermis) to the hands and feet (Figures 1 and 2). This dye deeply stains both nails and epidermis and is therefore extremely difficult to remove. Pulse oximetry in henna-stained digits can give extremely variable saturation results despite good readings on the accompanying plethysmograph trace. Some arterial oxygen saturation readings can be 5–10% below expected. Because henna dye is used on both the fingers and toes, this markedly decreases the access sites for this extremely useful mode of monitoring.

Roger Goucke, FFARACS
King Khalid National Guard Hospital
P.O. Box No. 9516
Jeddah 21423
Kingdom of Saudi Arabia

Figure 1. Henna staining of nails and terminal phalanges.

Figure 2. Henna staining of palmar surface of hand.

Reference

1. Coté, Goldstein EA, Fuchsman WH, Hoaglin DC. The effect of nail polish on pulse oximetry. Anesth Analg 1988;67:683–6.

Cut-off Values and Aspiration Risk

Key Words: GASTROINTESTINAL TRACT, STOMACH—pH and volume. COMPLICATIONS, ASPIRATION—gastric pH and volume.

To the Editor:

Abe et al. state that "it is generally agreed that a gastric pH lower than 2.5 and a gastric volume of 25 mL are capable of producing severe pulmonary damage" (1). While it may be generally accepted, it is not necessarily correct. "Accepted" cut-off values have been handed down through the literature until they have attained the aura of truth by sheer repetition. There are four major resons why this approach is invalid:

Vague origins. Roberts and Shirley, citing unpublished data, reported a cut-off value of 0.25 mL/kg of 0.1 N HCl in the Rhesus monkey (2). Teabeault made a cryptic reference to 25 mL following his report on aspiration pneumonitis in 2.5 kg rabbits (3).

The pH cut-off also seems to have been derived from Teabeault's work with rabbits. Unfortunately, the cut-off appears to be species-specific, and the critical value for humans is not known, although a small (only 10 patients) series places it in this general range (4). James et al. demonstrated what common sense would dictate: pulmonary damage following acid aspiration is a function of both pH and volume (5).

Faulty statistics. Volume and pH are on an interval scale. The unpaired *t*-test is the proper hypothesis test for interval scale data from two treatment groups (6). Is 2.4 so much different from 2.6 that it deserves a separate category? Is 24 mL that different from 26 mL?

Zero offset. Since blind nasogastric tube evacuation of the stomach leaves a residual (7), there is probably a nonzero offset for all studies utilizing this method, which invalidates rigid adherence to volume cut-offs.

Incomplete regurgitation. Even if the stomach contains >25 mL of liquid, it is highly unlikely that 100% of this material will be regurgitated and aspirated.

Let's cease referring to "generally accepted" truisms in favor of proper statistical treatment and a commonsense approach to the evaluation of risk of aspiration.

Michael S. Gorback, MD
Department of Anesthesiology
Duke University Medical Center
Box 3094
Durham, NC 27710

References

1. Abe K, Shibata M, Demizu A, Hazano S, Sumikawa K, Enotmoto H, et al. Effect of oral and intramuscular famotidine on pH and volume of gastric contents. Anesth Analg 1989;68:541–4.

2. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–68.

3. Teabeault JR. Aspiration of gastric contents. An experimental study. Am J Pathol 1952;28:51–67.

4. Lewis RT, Burgess JH, Hampson LG. Cardiorespiratory studies in critical illness. Changes in aspiration pneumonitis. Arch Surg 1971;103:335–41.

5. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration—effects of pH and volume in the rat. Anesth Analg 1984;63:665–8.

6. Glantz SA. Primer of Biostatistics. New York: McGraw-Hill, 1981:314.

7. Taylor WJ, Champion MB, Barry AW, Hurtig JB. Measuring gastric contents during general anesthesia: evaluation of blind gastric aspiration. Can J Anaesth 1989;36:51–4.

A Buccal Sensor for Measuring Arterial Oxygen Saturation

Key Words: MEASUREMENT TECHNIQUES, OXIMETRY.

To the Editor:

Having experienced many of the problems described by the authors, I read with interest the report by Jobes and Nicolson (1) of a tongue sensor for monitoring arterial oxygen saturation. However, I was frustrated in my efforts to apply their technique, especially in small infants. The presence of multiple appliances and copious secretions in a small oral cavity made application of the tongue probe extremely difficult. Of greater concern, I experienced several instances in which the probe worked its way loose from the tongue during the course of surgery. In an effort to avoid these problems, I modify the probe by using the

somewhat stiffer malleable metal from the bridge of an oxygen mask and apply it across the lip at the corner of the mouth. This "buccal" sensor seems to offer the advantage of the tongue sensor in terms of reliable monitoring of oxygen saturation even in the presence of arterial vasoconstriction or low cardiac output. More importantly, it is extremely easy to apply and stays reliably in place. Given the importance of arterial oxygen saturation monitoring in modern practice, it is imperative that reliable monitoring sensors and sites be available. The buccal sensor may offer an alternative when other sites are impractical or unreliable.

Joel B. Gunter, MD
Washington University School of Medicine
St. Louis, MO 63110

Reference

1. Jobes DR, Nicolson SC. Monitoring of arterial hemoglobin oxygen saturation using a tongue sensor. Anesth Analg 1988;67:186–8.

Figure 1. The CBPS showing the air chamber (solid arrow) that is connected to an aneroid manometer and the fluid filled chamber (open arrow) that is connected to pressure monitoring tubing and then to the arterial line.

Monitoring Effective Chest Compression during Cardiopulmonary Resuscitation

Key Words: MONITORING, BLOOD PRESSURE—disposable device. BLOOD PRESSURE, MONITORING. EQUIPMENT, BLOOD PRESSURE MONITOR.

To the Editor:

Effective external cardiac compression is a critical component of cardiopulmonary resuscitation (CPR). An effective and practical method of optimizing chest compression during CPR is the Continuous Blood Pressure Surveillance device (CBPS) (Pressurveil, Concept Inc., Clearwater, FL).

The CBPS is a light, disposable, and sterilely packaged device that can be kept on the resuscitation cart and requires minimal preparation for immediate use. The device consists of two small chambers separated by a pliable diaphragm housed in a plastic casing. One chamber (Figure 1, open arrow) is fluid filled, the other (Figure 1, solid arrow) air filled. The fluid filled chamber is joined to the arterial catheter with a stopcock by a length of connecting tubing, whereas the air chamber interfaces with a standard aneroid manometer (Figure 2). Blood pressure is mechanically transduced across the air fluid interface to display arterial pressure on the manometer. The device will only reliably read mean arterial pressure as damping occurs between the unit's air-liquid chamber interface (1).

Currently, the primary use of the CBPS is monitoring arterial pressure during patient transport from the operating room. The blood pressure of patients who have cardiac arrests in hospital settings where immediate access to invasive monitoring is impossible can be quickly monitored with the CBPS. A member of the arrest team insets an arterial catheter that is then linked with standard connect-
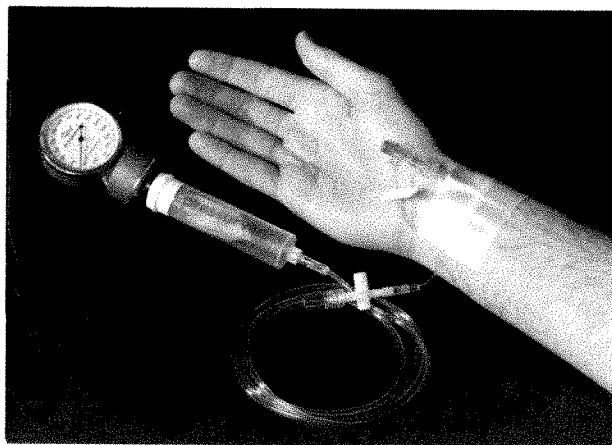
Figure 2. The CBPS monitoring pressure in the radial artery. Note the linkage of the fluid filled chamber with the arterial line via a stopcock and connecting tubing.

ing tubing to the CBPS (Figure 2). Preparation consists of flushing a few mL of sterile heparinized saline solution into the fluid port.

With the monitor positioned at the level of the right atrium, mean arterial pressure readings can be constantly obtained from the aneroid gauge. In addition, samples for measurement of arterial blood gas tensions can be drawn from an added in-line stopcock.

This simple system has been in use at our institution during cardiac arrests in settings removed from the intensive care unit or operating room and has served as an excellent guide to the adequacy of external chest compression. Mean resuscitative blood pressures of 60-mm Hg are generated with effective sine-wave cycled compressions. The individuals performing CPR can fine tune (in the case of some individuals, grossly change) their compression technique to generate a suitable pressure. Duration of compression is an important aspect of CPR (2) and the CBPS can demonstrate lower mean pressure

during the "jerky" compressions that characterize some efforts.

We have compared the pressure readings obtained with the CBPS with those obtained simultaneously from electromechanical transducers attached to the same arterial catheter and found a very close correlation of the mean arterial pressure. Although its use does not eliminate the employment of precise arterial monitoring when available, the device is an inexpensive, practical, and accurate means to a potentially considerable clinical benefit during CPR. Once restoration of sustaining cardiac activity has been established, infusions of vasopressors can be given with greater precision pending the transfer of the patient to an intensive care area.

Factors such as obesity, hypotension, and improper cuff fit that mitigate against accurate auscultative blood pressures can also be corrected.

Miles Dinner, MD
Department of Anesthesiology,
The New York Hospital, Cornell University Medical
    College,
New York, NY 10021.

References

1. Ramsey M. A disposable pressure monitoring system. Anesth Analg 1973;52:868–9.

2. Taylor GJ, Tucker WM, Green HL, Rudikoff MT, Weisfeldt ML. Importance of prolonged compression during cardiopulmonary resuscitation in man. N Engl J Med 1977;296:1515–7.

Difficult Intubation in Severe Diabetics

Key Words: COMPLICATIONS, DIABETES—tracheal intubation. INTUBATION, TRACHEAL.

To the Editor:

Hogan et al. (1) report a startlingly high and heretofore unappreciated 40% incidence of difficult laryngoscopy in a group of severe diabetics. If this phenomenon is confirmed, it will be an important contribution to decreasing intubation-related morbidity.

A few important but obtainable factors were not mentioned in the paper. Which laryngoscope blades were used? Was correct sniffing position employed? Who was doing the laryngoscopy—residents, nurse anesthetists, or attendings? Was the extent of relaxation confirmed, or at least had an adequate dose of relaxant been given? Were simple and effective maneuvers such as posterior and superior displacement of the larynx tried?

Although the 0.5% institutional rate of difficult laryngoscopy is admirable and in line with published rates, the skeptical reader might wonder whether this unblinded, retrospective study could have been subject to a departmental conviction that diabetics posed difficulties during intubation. The authors seem correct in stating that there was no *selection* bias, but the possibility of other preconceptions among members of their department is not so easily

dispelled. For example, it is possible that being apprehensive or flustered when approaching an intubation might have left the intubator less adept. Unconscious bias might have prevented laryngoscopists from optimally positioning the head, a very common cause of failed intubation in a patient with normal anatomy (2,3).

From years of watching nurse anesthetists and residents intubate, it is my opinion that identifying whether the laryngoscopy is truly difficult (versus a problem with the conditions or the intubationist) is not an "explicit" task, but rather requires judgment and therefore may admit bias.

Ronald M. Meyer, MD
Columbus Hospital
Chicago, IL 60614

References

1. Hogan K, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988;67:1162–5.

2. Finucane BT, Santora AH. Principles of airway management. Philadelphia: F. A. Davis, 1988:144.

3. Latto IP, Rosen M. Difficulties in tracheal intubation. Philadelphia: Baillière Tindall, 1985:110.

Difficult *Laryngoscopy* and Diabetes Mellitus

In Response:

Ronald Meyer ("Difficult Intubation in Severe Diabetics," Anesth Analg 1989;69:419) is correct in observing that a few factors pertinent to difficult laryngoscopy in diabetes mellitus were not mentioned in our study. We did consider the items he lists, of course, and many others as well. A retrospective search, however, is constrained by the limitations of chart review. Often, readily available data are of no apparent value. For example, what useful conclusions can be drawn from the inventory of laryngoscope blades used in our study (Table 1)? Other factors (sniffing position, degree of relaxation, displacement maneuvers) defy meaningful classification in an ex post facto analysis. Hence, there is no alternative but to assume adherence to equivalent standards of care in matching categories. In every instance, laryngoscopy was under the direct supervision of the attending anesthesiologist. When difficulties arise, here, as in other institutions, the laryngoscope is passed to the individual with the most experienced hand, who is responsible in turn for the accuracy of notations alerting subsequent anesthesiologists.

The association of airway disasters with pancreas transplantation was apparent early on, in part, because of the novel and highly experimental nature of the surgery. A departmental conviction that pancreas recipients pose special hazards, therefore, was disseminated. Pancreas-transplant patients were approached with trepidation and, if anything, greater attention to the details of laryngoscopy throughout the remainder of the study period.

Meyer's concern for unconscious bias on the part of anesthesiologists flustered in the care of kidney recipients is more easily dispelled. Because all pancreas candidates

Table 1. Laryngoscope Blades Used for Intubation

Operation	Macintosh 3	Macintosh 4	Miller 2	Miller 3	Other[a]	Totals
Cadaver renal transplant						
Diabetic: routine laryngoscopy	19	0	4	1	1	25
Diabetic: difficult laryngoscopy	11	1	1	4	1	18
Non-diabetic: routine laryngoscopy	62	1	3	1	5	72
Non-diabetic: difficult laryngoscopy	1	0	1	0	0	2
Living-related renal transplant						
Diabetic: routine laryngoscopy	20	1	3	1	1	26
Diabetic: difficult laryngoscopy	4	0	0	1	1	6
Non-diabetic: routine laryngoscopy	31	0	3	0	3	37
Non-diabetic: difficult laryngoscopy	1	0	0	0	0	1
Pancreas transplant						
Diabetic: routine laryngoscopy	21	0	0	0	3	24
Diabetic: difficult laryngoscopy	11	0	2	0	3	16
Totals	181	3	17	8	18	227

[a]Phillips or Wisconsin blades, fiberoptic intubation, tracheostomy, or unrecorded.

had prior kidney transplantation, our hypothesis was that airway complications were somehow correlated with high dose steroid or other immunosuppressant regimens in this group. As we prepared our report on pancreas recipients, it became clear that a control population, the renal recipients, was called for. The interval sampled for renal recipients had since passed, and no thought of difficult laryngoscopy in this population was evident during the sampling interval or tabulation of the data. Data from the kidney recipients refuted our initial hypothesis, raising others discussed in our work.

How could a 32% incidence of difficult laryngoscopy in diabetic kidney recipients have gone unnoticed? Perhaps an answer may be found in consideration of the numbers involved. Our center performs about 200 kidney transplants a year; therefore, a staff anesthesiologist might perform eight, of which about one-half or fewer of the recipients would have diabetes. Of these, one or two would be predicted to have difficult laryngoscopy, and this number could easily go unrecognized amidst a busy annual practice. Only through retrospective search can the occurrence of rare events and associations be brought into relief. Only through prospective, blinded investigations, however, can the incidence be known with precision, and the contribution of factors such as those cited by Meyer be addressed.

Since submission of our work, two studies, confirming our observations have come to our attention. Orko et al. (1) found it impossible to see the vocal cords in 6 of 20 diabetic patients anesthetized for renal transplantation. In a retrospective search (2), difficulties in endotracheal intubation were encountered in 19% of diabetic isolated kidney recipients and in 29% of diabetic pancreas and kidney recipients.

Finally, we would like to underscore the difference between laryngoscopy and tracheal intubation. Although one is ordinarily preliminary to the other, the two are quite distinct in skills, assessment, and associated conditions. Blind intubation may be easy, whereas a direct view of the vocal cords is impossible. Conversely, it may be possible to see the larynx but not intubate the trachea because of subglottic obstruction, tracheomalacia, and so forth. As knowledge of laryngoscopy acquires a firmer scientific basis, it will be important to avoid confusion on this point.

Kirk J. Hogan, MD
Deborah Rusy, BS
Scott R. Springman, MD
Department of Anesthesiology
University of Wisconsin
Madison, WI 53792

References

1. Orko R, Heino A, Bjorksten F, Scheinin B, Rosenberg PH. Comparison of atracurium and vecuronium in anaesthesia for renal transplantation. Acta Anaesthesiol Scand 1987;31:450–3.

2. Eleborg L, Norberg A. Are diabetic patients difficult to intubate? Acta Anaesthesiol Scand 1988;32:508.

CO_2 Levels during Opioid Reversal with Naloxone

Key Words: ANTAGONISTS, NARCOTIC—naloxone.

To the Editor:

I enjoyed reading the well-designed study of Mills et al. (1), addressing the cardiovascular effects of fentanyl reversal by naloxone at varying arterial CO_2 tensions in dogs. However, I have strong reservations concerning the conclusion drawn from their data and "the recommendation that normocapnia or slight hypocapnia should be established before naloxone is administered to the postanesthetic patient."

Naloxone is most often administered at the end of an anesthetic to restore adequate spontaneous ventilation. The normal major physiologic stimulus for breathing in human patients is CO_2. All patients emerging from anesthesia require higher than normal arterial (and brain) CO_2 tensions to breathe adequately. Even with relatively large doses of opioids, it has been shown that narcotic reversal is not always needed (2). In patients who require reversal, much smaller doses than those studied by Mills et al. (1) are

almost always adequate when carefully titrated to effect. Mills et al. (1) did not find any difference in the increases in heart rate response to naloxone (0.4 mg) in any of their groups of dogs, and the increase in mean arterial pressure after naloxone was also similar whether or not the dogs were hypercapnic or not. Admittedly, the increase in blood pressure after administration of naloxone in the hypercapnic dogs was the greatest in absolute terms and considerably above baseline levels. Clinically, increases in heart rate and blood pressure are our chief concern when reversing the effects of opioids. I do not believe their findings with regards to heart rate and blood pressure justify their clinical recommendation, especially when lower but still effective doses may have produced no differences between the groups.

The suggestion that normocapnia or hypocapnia should be established before naloxone is administered goes against the grain of sound anesthetic practice for other reasons too. Hyperoxic hypoventilation is widely used to establish adequate ventilation in patients at the end of a procedure. This allows patients to develop a CO_2 tension adequate to initiate spontaneous ventilation. If patients were kept normocapnic or hypocapnic at the end of an anesthetic course, many would receive naloxone while their $Paco_2$ was below their apneic threshold. Because of this "low $Paco_2$" and the lack of chemical stimulus to breathe, a larger than necessary dose of naloxone would often be needed to shift the brainstem's response to CO_2 to where breathing would start and be adequate. Indeed, under these circumstances, possibly all patients who are given an opioid might receive naloxone, thereby generating more problems (e.g., pain and adverse hemodynamic consequences) than the naloxone would solve.

A more subtle reason behind the method of hyperoxic hypoventilation is to test for the "apneic threshold" or how "narcotized" a patient really is. It is well known that recurarization is less likely to occur when reversing the effects of muscle relaxants if some response can be elicited by peripheral nerve stimulation before administration of a reversal agent. Similarly, one can be more confident that renarcotization will not occur if some spontaneous respiratory effort is present before the administration of naloxone. Maintaining normocapnia or slight hypocapnia at the end of anesthesia would preclude clinical assessment by hyperoxic hypoventilation of the degree of narcotization and respiratory depression. The administration of naloxone could not be carefully titrated in conjunction with the normal chemical stimulus to breathe, but would be rather empiric. This empiric administration would likely result in an increased incidence of overdosage and underdosage. In addition, once patients received naloxone and were extubated, they would not have their ventilation assisted and CO_2 would accumulate and possibly produce the same effects clinicians hoped to avoid.

On the other hand, one could construe the recommendation of Mills et al. (1) to imply that after hyperoxic hypoventilation has been tried and opioid reversal is thought necessary, one should reinstitute hyperventilation

to attain normocapnia or slight hypocapnia before naloxone reversal. This maneuver would allow one to test for the "apneic threshold," but would consume extra time and still might lead to larger than necessary doses of naloxone being given.

Finally, the response of the dog to fentanyl is markedly different from that of human patients (3). I retain a considerable degree of skepticism about anesthetic implications made for humans but drawn from data in dogs, especially with regards to opioids.

Peter L. Bailey, MD
Department of Anesthesiology
University of Utah School of Medicine
50 N. Medical Drive
Salt Lake City, UT 84132

References

1. Mills CA, Flacke JW, Muller JD, et al. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. Anesth Analg 1988;67:730–6.
2. Bailey PL, Clark NJ, Pace NL, et al. Antagonism of postoperative opioid-induced respiratory depression: nalbuphine vs. naloxone. Anesth Analg 1987;66:1109–14.
3. Bailey PL, Port DJ, McJames S, Reinersman L, Stanley TH. Is fentanyl an anesthetic in the dog? Anesth Analg 1987;66:542–8.

In Response:

We appreciate the opportunity to respond to Dr. Bailey's letter. It appears that his major concern is with our rather restrained clinical recommendation on the use of naloxone, which was based on our investigation of the hemodynamic and adrenergic responses to naloxone reversal of fentanyl in the presence of varying arterial CO_2 tensions in dogs. Although no animal experiment can translate exactly to the clinical situation, it may be possible and is customary to achieve a better understanding of events in animal models. Therefore, we attempted to explore the possible causes of the admittedly rare episodes of hypertension, life-threatening cardiac arrhythmias, pulmonary edema, and other adverse hemodynamic events after reversal of narcotics with naloxone (references 1 to 10 in our report). Most of these reports did not specify the patient's blood gas tensions at the time of naloxone administration. One testable hypothesis was that the hypercapnia often present before reversal of narcotic-induced respiratory depression would on sudden reversal, cause the known responses to hypercapnia to come into play. Indeed, we did see that there was significantly more hypertension and significantly higher plasma catecholamine levels in the presence of hypercapnia.

Concerning the first point raised in Dr. Bailey's letter, we do agree, and did so state, that there were no significant differences in heart rate among our groups of dogs, although the trend was toward a higher heart rate in normocapnic and hypercapnic dogs than in hypocapnic ones (mean values of 160 beats/min in the former two and 125 beats/min in the latter). As we attempted to explain, the continuation of general anesthesia in these dogs, as well as the accompanying direct depressant effects of an elevated CO_2 tension on the circulation (see Table 1 and reference 32

in our report) may have prevented a greater increase in heart rate from occurring after sudden narcotic reversal under hypercapnic conditions. In addition, the vasodilation caused by the direct action of CO_2 may have prevented even greater differences in blood pressure between the hypercapnic and the other animals. In other words, in the hypercapnic dogs, the stimulus for a fast heart rate and higher blood pressure was present (as indicated by the concomitant marked increases in plasma catecholamine levels in this group), but the simultaneous direct depressant action of the elevated Pco_2 to some extent counteracted the indirectly mediated excitatory manifestations. (See Bendixen et al. (1) for further discussion of the direct effects of CO_2 on the canine cardiovascular system.)

Dr. Bailey's next point concerns the large dose of naloxone used. Because we were well aware of the fact that dogs generally require greater doses of CNS drugs to achieve the same effect (to our knowledge, a quantitative rather than qualitative difference in response from humans), we gave our animals 50 μg/kg fentanyl, certainly more than one might need during the usual "balanced" anesthesia in patients. Similarly, having given more fentanyl, we had to give more naloxone for a competitive antagonism, but the doses used were not in the ball park of the nonpharmacologic "megadoses" reported by many authors. We used "supramaximal" doses for pharmacologic antagonism of the narcotic in this investigation, because it was our stated purpose to achieve maximal antagonism. (The anesthetized animals were not in pain so no residual narcotic effect was necessary.) We were not advocating using a 20 μg/kg dose of naloxone in patients. Indeed, we have often recommended that naloxone be administered in very small (1.5 μg/kg) increments. We do not think, however, that this invalidates our findings of differences in circulatory and adrenergic responses to naloxone in different ventilatory situations. After all, many of the reported adverse reactions occurred after small doses.

Dr. Bailey continues with concerns about our recommendation that hypercapnia, which is likely to be present at the conclusion of an anesthetic, should be avoided during the administration of naloxone to the postanesthetic patient. The reason he gives for this statement is that hypercapnia provides the needed stimulus to breathe at the end of the operation, and that administration of naloxone in the absence of this stimulus "would likely result in an increased incidence of overdosage and underdosage." We are convinced that the opposite is true. Carbon dioxide tension is the most important stimulus to respiration. However, during awakening from anesthesia, it is certainly not the only one (e.g., pain, awareness). Nor do we agree that "all patients emerging from anesthesia require higher than normal arterial CO_2 tensions to breathe." Some do, however. Dr. Bailey seems to assume that we were advocating giving naloxone to all emerging patients without first attempting to ascertain the patient's "apneic threshold" (i.e., ventilatory response to an elevated end-tidal CO_2 tension). We did not! On the contrary, we suggested that only patients *with* an elevated $Paco_2$, (i.e., those in whom

the "apneic threshold" had been already demonstrated by capnography to be unacceptedly elevated) should not be given naloxone until their CO_2 tensions had been lowered to normal or slightly below normal levels, a matter of only a very few minutes in most cases. In our own practice of anesthesia, there appears to be ample time to accomplish this during wound closure and dressing placement. Through the response of the patient to surgical stimulation, and the type, timing, and dosage of the narcotic used, we believe we have an idea of how close we are to being correct in our estimation of residual opioid effects. In a very brief time, through intentional hypoventilation, we can determine if the patient will, in fact, breathe at an acceptable end-tidal CO_2 tension. If not, a short time of hyperventilation will restore arterial CO_2 tension to normal or below normal, and we can proceed with narcotic reversal.

From Dr. Bailey's comments, it would seem that he believes that narcotic reversal should be carried out under conditions of hypercapnia so that patients will retain this stimulus to breathe and, therefore, not receive too much naloxone. We maintain that it is undesirable, if not dangerous, even from the point of view of respiration only (apart from the increased cardiovascular and adrenergic stimulation that we demonstrated in these experiments), to administer naloxone in the presence of hypercapnia. As Dr. Bailey knows, the CO_2 response curve is shifted to the right and its slope is depressed in the presence of opioids. When normal sensitivity is restored suddenly, the curve is shifted back to the left and its slope increases. Therefore, if naloxone is administered in the presence of hypercapnia, the consequence will be marked hyperventilation until the elevated Pco_2 is reduced to the appropriate level. This new equilibrium point is not predictable from the original hyperventilatory response and, thus, naloxone administration may still leave the patient with an undesirably high Pco_2. One of us (W.E.F.) has demonstrated this sequence to generations of medical students to impress upon them that temporary hyperventilation is the inevitable consequence of reversal of opioid-induced hypercapnia. Thus, determination of the correct dose of naloxone is not possible in the presence of hypercapnia.

Another point that must be emphasized is that many of the patients reported in the literature to have had adverse cardiovascular responses to reversal may have had much higher blood CO_2 levels than the rather mild hypercapnia ($Paco_2$ of 60 torr) that we used in our dog model. We have seen patients who were given naloxone when their arterial Pco_2 was more than 80 torr, especially in the days before routine end-tidal monitoring. Unlike the anesthetized dogs, many of the patients also will experience pain on reversal, and this would be expected to potentiate the respiratory and hemodynamic effects observed. As stated above, the elevated CO_2 tension stimulates respiration immediately after reversal, but it also represents a large number of milliliters of CO_2 in the total body, approximately 1 mL·kg·mm Pco_2. Thus, patients who are reversed from extreme hypercapnia may actually ventilate well for several minutes, but their ventilation will decrease as they

approach a new steady state. This new ventilatory state may still be somewhat depressed, and may cause problems later on. Therefore, having the patients at approximately the desired Pco_2 before reversal will allow a much better respiratory assessment. Finally, it is difficult to fine tune the reversal of narcotics with naloxone because the half-life is shorter than that of most narcotics. Thus, even if we produce exactly the right degree of reversal, this level can only be maintained for a few minutes, and will be followed by returning depression. The use of naloxone at a time when the Pco_2 is normal would be expected to allow for more disparity in the half-lives of the two drugs.

As far as the clinical situation, we are the last to recommend anything that would lead to overuse of naloxone. In fact, the first choice of some of us (C.A.M., J.D.M.) might be an agonist-antagonist in an effort to avoid many of the central stimulatory effects known to accompany complete narcotic reversal (2). However, whether or not the need exists for pharmacologic correction of respiratory depression can be determined only if Pco_2 is in an acceptable range before reversal.

Christopher A. Mills, MD
Joan W. Flacke, MD
Jordan D. Miller, MD
Werner E. Flacke, MD
Department of Anesthesiology
University of California–Los Angeles
Center for the Health Sciences
Los Angeles, CA 90024-1778

References

1. Bendixen HH, Laver MB, Flacke WE. Influence of respiratory acidosis on the circulatory effects of epinephrine in dogs. Circ Res 1983;13:64–70.

2. Flacke JW. Antagonism of opioid analgesics with nalbuphine and naloxone. In: Seminars in Anesthesia. Philadelphia, PA: Grune and Stratton, 1988;7:178–91.

Time-Dependent Changes in Bupivacaine Pharmacokinetics

Key Words: PHARMACOKINETICS, LOCAL ANESTHETICS—bupivacaine. ANESTHETICS, LOCAL—bupivacaine.

To the Editor:

I read with interest the recent report by Mazoit et al. (1), describing the clearance characteristics of bupivacaine after short and prolonged intravenous infusion. They commented that our pharmacokinetic data on prolonged infusions are contradictory (2,3). Our first report (2) involved only patients with chronic pain; our second (3) involved patients being treated for postoperative pain. In the group of patients with chronic pain, there was no change in serum α-1-acid glycoprotein concentrations over the course of perineural infusions of bupivacaine. α-1-acid glycoprotein is of paramount importance in regulating the extent to which bupivacaine is bound to serum proteins. Because the clearance of bupivacaine is dependent on the unbound

concentration of drug, and the concentrations of α-1-acid glycoprotein did not change in this group of patients, we reported that clearance of bupivacaine appeared to be constant from 24 h to several days (2). On the other hand, patients with postoperative pain had a significant increase in serum concentrations of α-1-acid glycoprotein over the first several postoperative days (3). It is true that bupivacaine concentrations accumulated over the 3-day study. However, bupivacaine clearance decreases with increasing serum levels of α-1-acid glycoprotein (2). Thus, pharmacokinetic conclusions of our two studies are not contradictory.

Mazoit et al. (1) also misinterpreted our findings when we gave prolonged perineural infusions to patients with chronic pain. In the study, we described a method of determining patient-specific clearance and elimination rates from two blood samples drawn 3 to 5 and 24 hr after the start of infusion. Mazoit et al. (1) commented that we reported no change in clearance between 3 and 24 hr (2). This is incorrect. Our estimate of clearance was made only from the 24-hr blood sample. The sample drawn 3 to 5 hr after the start of the infusion was used in conjunction with clearance to estimate the patient-specific elimination rate. By using only the 24-hr sample in our estimation of clearance, we were unable to determine whether bupivacaine exhibited time-dependent changes in clearance.

Finally, I do not agree with the authors' conclusion that the increased elimination half-life observed by Mazoit et al. (1) in the prolonged infusion group is not, at least in part, caused by a time-dependent increase in volume of distribution. We reported (4) that bupivacaine does exhibit such a time-dependent change in pregnant patients receiving epidural infusions for several hours. The protocol used by Mazoit et al. (1) involved blood sampling only 1 hr before completion of a 24-hr infusion and again for several hours thereafter. Thus, time-dependent changes in volume of distribution over the course of the infusion cannot be evaluated. In addition, it would be of interest to know whether additional kinetic changes occur at 48 and 72 hr during prolonged intravenous infusion in the canine model. Such an evaluation would allow a more direct comparison with the data we obtained in human patients (2).

Donald D. Denson, PhD
Department of Anesthesia
University of Cincinnati College of Medicine
Cincinnati, OH 45267-0531

References

1. Mazoit JX, Lambert C, Berdeaux A, Gerard JL, Froideveaux R. Pharmacokinetics of bupivacaine after short and prolonged infusion in conscious dogs. Anesth Analg 1988;67:961–6.

2. Denson DD, Raj PP, Saldahna F, Finnsson RA, Ritschel WA, Joyce TJ. Continuous perineural infusion of bupivacaine for prolonged analgesia: pharmacokinetic considerations. Int J Clin Pharmacol Toxicol Ther 1983;21:591–7.

3. Raj PP, Knarr D, Hartrick CT, Pither CP, Denson DD, Hopson CN. Efficacy of continuous epidural bupivacaine infusion for postoperative pain relief. Anesthesiology 1984;61:A186.

4. Denson DD, Knapp R, Turner PA, Thompson GA. Serum bupivacaine concentrations in term parturients following continuous epidural infusion for labor and delivery. Ther Drug Monitoring 1984;6:393–8.

n Response:

n his letter, Denson disagrees with some assertions of our eport (1). The first point of concern is that the decrease in learance of bupivacaine observed by Raj et al. (2) may be xplained by a decrease in the free drug concentration in erum caused by the increase in α-1-acid glycoprotein oncentration during the postoperative period. We totally gree with this explanation, and it is why we said that their)atients were not in a steady state (1).

Our interpretation of the report by Denson et al. (3) epresents the second point of concern. We probably misnterpreted the authors findings when we said that 'Denson et al. suggested that bupivacaine clearance did lot change significantly between 3–5 hr after the start of an nfusion and its termination several days later." Among)ther things, we based our interpretation on the authors' tatements, such as: "This study demonstrates that two)lood samples drawn at 3–5 hr after the start of infusion nd at steady state are sufficient to accurately determine the learance rate for a patient." However, we believe that the nost important misinterpretation is based on the sense of he word contradictory: in our mind, it meant that the iterature is confusing on this subject, and that any com->arison between the studies is made difficult because some esults may differ because of differences in the methodol->gy.

Denson et al. pointed out the possibility that the oberved increased terminal half-life in the prolonged infuion group was at least partly a result of a time-dependent icrease in the volume of distribution. We did not exclude his possibility, but the decrease in clearance is ascertained y the data, whereas the increase in Vz with time is only ypothetical in our study. In his letter, Denson refers to a tudy done after epidural infusion of bupivacaine in partuients (4). In that study, the authors applied the method of :olburn (5) to data from the literature. They reported that ne half-life needed to achieve a steady-state volume of istribution for bupivacaine was approximately 1 hr. In ict, the method of Colburn is an alternative approach to fit ata with multiexponential characteristics; the rate contant(s) used to describe the time course of volume of istribution change is equivalent to the intercompartmental ite constants used for linear mammillary models. Denson t al. (4) applied the method of Colburn to epidural infusion f bupivacaine. In this case, the absorption process is iphasic (6), which makes any interpretation difficult be-ause k_a and k_v are dependent on each other (5).

Finally, as explained in the discussion section (1), early nd very late blood samples were not drawn because we referred a simple protocol in order to have limited but iterpretable data.

:an Xavier Mazoit, MD
\épartement d'Anesthésiologie
'niversité Paris-Sud, Hôpital Bicêtre
!275 Le Kremlin-Bicêtre Cedex, France

References

1. Mazoit JX, Lambert C, Berdeaux A, Gerard JL, Froidevaux R. Pharmacokinetics of bupivacaine after short and prolonged infusion in conscious dogs. Anesth Analg 1988;67:961–6.
2. Raj PP, Knarr D, Hartrick CT, Pither CP, Denson DD, Hopson CN. Efficacy of continuous epidural bupivacaine infusion for postoperative pain relief (abstr). Anesthesiology 1984;61:A186.
3. Denson DD, Raj PP, Saldahna F, Finnson RA. Ritschel WA, Joyce TJ. Continuous perineural infusion of bupivacaine for prolonged analgesia: pharmacokinetic considerations. Int J Clin Pharmacol Toxicol Ther 1983; 21:591–7.
4. Denson DD, Knapp R, Turner PA, Thompson GA. Serum bupivacaine concentrations in term parturients following continuous epidural infusion for labor and delivery. Ther Drug Monit 1984;6:393–8.
5. Colburn WA. A time-dependent volume of distribution term used to describe linear concentration-time profiles. J Pharmacokinet Biopharmacol 1983;11:389–400.
6. Burm AGL, Vermeulen NPE, van Kleef JW, de Boer AG, Spierdijf J, Breimer DD. Pharmacokinetics of lidocaine and bupivacaine in surgical patients following epidural administration. Simultaneous investigation of absorption and disposition kinetics using stable isotopes. Clin Pharmacokinet 1987;13:191–203.

Epidural Clonidine in Lower Limb Deafferentation Pain

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine. PAIN, DEAFFERENTATION.

To the Editor:

The treatment of deafferentation pain arising from peripheral nerve injury continues to present a major challenge in the pain relief clinic. We report the successful management of such a case with epidural administration of clonidine.

A 22-year-old man presented with complete dorsal column and spinothalamic loss in the left L5–S2 distribution after a stab wound in the left, fourth lumbar paravertebral area. He was referred after developing a severe lancinating pain in his left foot, which had been unresponsive to conventional simple analgesics or carbamazepine. A myelogram performed demonstrated the disrupted nerve roots, but no other obvious pathology (Figure 1). The pain was not improved with either transcutaneous electrical nerve stimulation or a series of intravenous sympathetic blocks of the affected limb. The epidural injection of clonidine (150 μg in 5 mL of normal saline solution) was therefore carried out at the L4-L5 interspace. This resulted in a dramatic improvement in his symptoms over the next 24 hr, which persisted thereafter so that he was able to return to work 3 wk later. The pain has remained well controlled in the subsequent 12-mo period.

Deafferentation pain may arise in any part of the body where the flow of afferent impulses has been partially or completely interrupted, whether by trauma or other pathologic processes (1). The changes associated with such disruption occur not only at the injury site, but also within the central nervous system (2), often making treatment difficult, particularly if delayed. Most success has been claimed with transcutaneous electrical nerve stimulation and from regional and sympathetic nerve blocks combined

Figure 1. Myelogram obtained at admission, demonstrating the divided nerve roots of the cauda equina (**arrow**).

with a program of exercise and physiotherapy (1). Recent attention has, however, focussed on the antinociceptive activity of clonidine (3), an α-2-adrenergic partial agonist. This agent has been shown to have considerable analgesic activity when administered intrathecally in animals (4) and when administered by epidural injection in human patients (5). In addition, the preoperative oral administration of clonidine can reduce both intraoperative anaesthetic and analgesic requirements (6). The mechanism of the antinociceptive action of clonidine is unclear, but appears to be mediated, at least in part, at spinal cord level and is

reversed by α-receptor blocking agents, but not by naloxone. The currently available parenteral injection solution in the United Kingdom (Catapres, 150 μg in 1 mL, Boehringer Ingelheim) is preservation-free and isotonic, with a pH of 4.0–4.5, making it suitable for epidural administration even though it is not yet licensed for this purpose.

There is no evidence that clonidine has neurotoxic effects (7,8), and the success of its use in this patient suggests that further controlled study of the technique may be valuable for this very disabled group of patients.

David M. Coventry, MB, ChB, FFARCS and
Gordon Todd, MB, ChB, FFARCS
Pain Relief Clinic
Institute of Neurological Science
Southern General Hospital
Glasgow G11 6NT, Scotland

References

1. Tasker RL. Deafferentation. In: Wall PD, Melzack R, eds. Textbook of pain. Edinburgh: Churchill Livingstone, 1985:119–32.

2. Schott GD. Mechanisms of causalgia and related clinical conditions: the role of the central and of the sympathetic nervous systems. Brain 1986;109:717–38.

3. Kulkarni SK, Mehta AK, Kunchandy J. Some noncardiovascular actions of clonidine. Drugs Today 1984;20:497–507.

4. Reddy SVR, Maderdrut JL, Yaksh TL. Spinal cord pharmacology of adrenergic agonist-mediated antinoception. J Pharmacol Exp Ther 1980; 213:525–33.

5. Tamsen A, Gordh T. Epidural clonidine produces analgesia. Lancet 1984;2:231–2.

6. Flacke JW, Bloor BC, Flacke WE, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. Anesthesiology 1987;67:11–9.

7. Coombs WD. Allen C, Meier F, Fratkin J. Chronic intraspinal clonidine in the sheep (abstr). Reg Anesth 1984;9:47.

8. Tamsen A, Gordh T. Clonidine is not neurotoxic. Lancet 1984;2:876.

Book Reviews

The Yearbook of Anesthesia 1988

R. D. Miller, R. R. Kirby, G. W. Ostheimer, M. F. Roizen, R. K. Stoelting. Chicago: Year Book Medical Publishers, 1988, 367 pp, $45.00.

The 1988 Yearbook of Anesthesia successfully continues its 24-year tradition of providing a concise yet comprehensive review of clinical and scientific literature as it relates to anesthesia. The editors abstract anesthesia-relevant articles from 99 medical and allied health journals (emphasizing nonanesthesia publications) and present each with a commentary. The format, similar in all Yearbook series, remains unchanged. The book is loosely organized into 15 chapters that are further subdivided into separate topics.

Anesthesia practitioners with a variety of interests and experience will benefit from the breadth and depth of the literature reviewed. The spectrum of subjects includes basic science, such as genetic analysis of halothane sensitivity in bacteria; practical material such as the utility of pulse oximetry in neonates; and controversial issues, including the role of heroic measures in terminally-ill patients. The concise format enables the reader to enjoy learning about such diverse topics. One must, of course, rely on the editors' choice of developments and articles worthy of inclusion. However, in general the literature selection is well balanced and particularly good in each editor's area of expertise. For example, the chapter on Critical Care by Drs. Kirby and Miller is outstanding because a variety of subjects are clearly presented and the material gives insight into new issues in critical care. On the other hand, pediatric and neuroanesthesia do not receive much emphasis, perhaps because these subspecialties are not represented on the editorial board.

A unique strength of the Yearbook is the editorial comments, which, in many cases, are more informative than the abstracts themselves. The editors' license to express opinion gives insight into their biases and practices and allows them to interject refreshing bits of philosophy and humor. The commentary also helps the reader to critically evaluate each topic and put it into a reasonable clinical context.

The only significant weakness of the book is the index. It is difficult to relocate specific abstracts using the index; easier cross-referencing is both possible and desirable. A minor issue is that the publisher's permanent advertise-ment on the back inside cover is too commercial for a textbook and should be eliminated.

In summary, the 1988 Yearbook of Anesthesia is an up-to-date, informative, concise, and easy to read review of literature pertinent to anesthesia. The spirit of the book is forward-looking, and the volume is well worth the modest investment.

Michele D. Szabo, MD
Gregory Crosby, MD
Massachusetts General Hospital
Boston, Mass.

Anesthesia in Obstetrics and Gynecology, Vol 3, No 1 of Problems in Anesthesia Series

DD Hood (ed). Philadelphia: JB Lippincott, 1989, 164 pp, $28.00 for single issue or $60.00 for annual subscription of four issues.

This text, actually 11 mini-reviews by 12 contributors, sets out from its preface "to present common obstetric problems . . . and develop courses of action" for the anesthesiologist. To this end, the chapter on diabetes is comprehensive yet succinctly written, and the chapter on preeclampsia contains a superb review of pathophysiology undergirding a strong case for the use of epidural anesthesia in these patients. Although the chapter on relatively rare orthopedic/neurological diseases might seem out of place in a text aimed at common problems, this is an inconsistency easily overlooked, given the delightfully concise handling of this typically dry topic. The chapter on similarly rare cardiovascular diseases, unfortunately, possesses no equally redeeming feature.

This collection reflects the widespread and justified enthusiasm for epidural anesthesia among obstetric anesthesia subspecialists. The advantages of epidural anesthesia in the management of obese and preeclamptic parturients are particularly well described. However, adoption of this management approach by the general anesthesiologist with marginal or remote training in epidural *technique* (much less the distinctive demands of an epidurally oriented labor ward) is surely a significant and common problem, but one that receives scant attention throughout the text. This reviewer suspects that this problem is not easily resolved, and the treatment that problem receives in

this text only heightens that suspicion. "The smaller volumes and weaker local anesthetics commonly used for labor analgesia," for example, are said to "potentiate inadequate block opportunities." Remedies involving administration of larger volumes and higher anesthetic concentrations are then described. However, the need for epidural dose minimization in obstetric anesthesia increases not inadequate block opportunities but rather the likelihood of uncovering deficiencies in technique, deficiencies that should first be corrected rather than submerged. The remedy should be exacting midline epidural technique, usually permitting the catheter to be threaded freely and without paresthesia, and thereby providing successful low-dose analgesia.

Acknowledgment in the preface that "obstetric problems present confusing and, at times, contradictory demands on the anesthesiologist" presages clarification on several fronts. However, there are notable disappointments. In every chapter dealing with the obstetric patient, antacid prophylaxis is called for because the pregnant patient is "at risk." However, references substantiating the clinical efficacy of this apparently stylish maneuver in improving outcome following aspiration are, after ten years of advocacy, nowhere to be found. This is in sharp distinction to the case for uterine displacement as a means of avoiding aorto-caval compression, wherein selected references from the massive amount of human data demonstrating the clinical importance of this concept are provided. At last, in the final chapter (on laparoscopic surgery), the other shoe drops: nonpregnant patients are also "at risk." Olsson et al. (1) reviewed the incidence of aspiration in over 185,000 anesthetics and found that obstetric cases were not overrepresented. If deacidification of pregnant women is worthwhile, all surgical patients should share in the blessings of such ablution.

But the last contributor also notes that "no convincing evidence exists that prophylactic therapy eliminates (or necessarily attenuates, according to this reviewer) pulmonary damage or reduces anesthesia-related mortality if aspiration occurs." Olsson and colleagues found that the incidence of aspiration was more than six times higher during the night than during daytime hours, and incriminated inexperienced airway management. In the obstetrical setting, there is a need for administration of anesthesia by adequately experienced anesthesiologists, the provision of proper equipment and assistance (including correctly applied cricoid pressure), the use of regional anesthesia whenever appropriate, and the avoidance of heavy sedation in labor. Unfortunately, these fundamentals are not expressed in this text with the enthusiasm afforded antacid prophylaxis. For general anesthesia in obstetrics, mask anesthesia has been superseded by rapid sequence intubation with cricoid pressure. The use of antacids is presently an interesting appendage to airway management, but neither theoretical justification nor good intentions can elevate it to "standard of care" without debasing the term.

The text suffers sporadically from ill-considered wording, an unbalanced expression of the contributor's personal preference, and an unchecked desire to define new standards of care. At one point it is reported that the ASA physical status classification "is used to assess 'risk' before anesthesia and surgery." In a paragraph addressing the risk of hypotension as a complication of epidural analgesia in the cardiac patient, it is noted in passing that "epinephrine is eliminated from local anesthetic solutions because of the possible effects on labor, blood pressure, and heart rate." Inasmuch as small doses of judiciously administered epidural epinephrine have not been shown to significantly affect any of these, one wishes the author would have elaborated on this thought before handing down a decision.

In summary, this text contains a few chapters that could justify its addition to a departmental library. For reasons discussed, those general anesthesiologists in need of basic information on this subject are not likely to be well served with this as an addition to their personal library. Certainly residents should *not* divert their attention from any of the several excellent textbooks on obstetric anesthesia.

Paul C. Youngstrom, MD
Case Western Reserve University
Cleveland, Ohio

Anesthesiology Clinics of North America Management of Postoperative Pain

Rollin V. Oden, MD, (ed). Philadelphia: W.B. Saunders Company, 1989, 262 pp, $69.00 annual subscription for four issues or $25.00 for single issue.

The editor of this text notes in the Preface that "because treating pain is *everybody's* business, it becomes *nobody's* business; leaving patients without any member of the medical team responsible for relieving their pain. The anesthesiologist should take the leadership role and become the *somebody* responsible for relieving acute pain."

The book comprises 15 well-written and well-organized chapters. Each chapter includes an extensive list of current references. In the opening chapters the reader is introduced to the problem of the undertreatment of acute pain and a review of mechanisms of pain transmission, pain modulation, and analgesia. Two chapters devoted to the pharmacology of opioid analgesics and their clinical use present a number of helpful guidelines for using these drugs. Chapters on patient-controlled analgesia and spinal analgesia review historical perspectives, clinical experience, techniques of administration, guidelines for management, and complications. A chapter on non-narcotic modalities emphasizes non-narcotic pharmacologic agents and neural blockade techniques. There are chapters on the management of pain following cesarean section delivery, following surgery on infants and children, and for victims of trauma and burns. Psychological issues of acute pain and the various psychological techniques for management are addressed in detail. Although psychological aspects are well recognized in chronic pain management, these chapters emphasize that little research or clinical attention is given to

these aspects of postoperative pain. A chapter on opioid-induced respiratory depression in the postoperative period reviews the literature regarding this side effect and notes the difficulty in evaluating the results of clinical studies on postoperative analgesia because of the lack of uniform study designs. Guidelines for designing a study are included. The book concludes with a chapter on the organizational and operational aspects of an acute pain service and a chapter on the consequences of postoperative pain and the physiological and psychological advantages of optimal pain control.

An unavoidable weakness in this multiauthored text is the degree of repetition in certain areas. The undertreatment of acute pain, opioid pharmacokinetics and pharmacodynamics, patient-controlled analgesia, and spinal anal-

gesia were discussed in a number of chapters. Also, a section on continuous intravenous narcotic infusions would have been beneficial to the reader.

The editor notes that a review of five major textbooks of surgery encompassing more than 10,000 pages of text found only seven pages devoted to postoperative pain treatment, with three of the books not addressing the issue at all. This text gives a comprehensive picture of the management of postoperative pain and will be valued by all disciplines active in acute pain management.

Russell T. Wall, MD
National Institutes of Health
Bethesda, Md

Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®
(vecuronium bromide) for injection

Minimizes
the variables

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

CARDIOVASCULAR EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

HISTAMINE SIDE EFFECTS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

METABOLIC CONSIDERATIONS

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Anesthesia and Analgesia

Contents

HU

Hahnemann University

Department of Anesthesiology

is sponsoring a one day symposium

Anesthetic Considerations for the Trauma Patient - 1989

Saturday, November 18, 1989

Sheraton Valley Forge Hotel   North Gulph Road and First Avenue   King of Prussia, Pennsylvania

Participating Faculty:

Brian Dalton, M.D.	Margaret Libonati, M.D.	Meir Mazala, M.D.	Michael Rhodes, M.D.
John G. Shutack, D.O.	Jerrold H. Levy, M.D.	Randolph D. Maloney, M.D.	Ruby Padoline, M.D.
Henry Rosenberg, M.D.	Janet N. Siler, M.D.	Daniel Teres, M.D., F.A.C.P.	

This seminar will update participant's knowledge about the anesthetic care of *the pregnant trauma victim, the head trauma patient,* and *the patient with opthalmological injury.* Aspects of managing trauma in relation to cost, transport, blood conservation, use of neuromuscular blockers, and anaphylactic reaction in critically ill patients will be covered.

For further information and application:

Office for Continuing Education
Hahnemann University
Broad & Vine, M.S. 623
Philadelphia, PA 19102-1192

(215) 448-8263

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1990 B.B. SANKEY
ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1990 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **January 15, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1990 Award(s) will be announced at the Annual Scientific Meeting (64th Congress) of the International Anesthesia Research Society to be held at the Sheraton–Waikiki Hotel, Honolulu, Hawaii, March 9–13, 1990.

SPECIAL ARTICLE

CLINICAL REPORTS

LETTERS TO THE EDITOR

If You're Looking For The Best Anesthesiology Billing and Practice Management System, We've Got Your Number.

1-800-2GET-NHS

Call us today, and we'll send you a free information kit on the best computer system designed exclusively for anesthesiologists — The ULTRA Anesthesiology Billing and Practice Management System from Northern Health Systems.

You'll receive all of the information you need to automate your growing practice.

Information that will improve the efficiency of your office and speed your cash flow.

You'll discover a feature-packed system that can give you instant patient information. Simplify your accounting. Process your claims electronically. Produce customized reports. And much, much more.

Call us toll-free at 1-800-2GET-NHS for your free information kit. It's the only number you need.

NHS Northern Health Systems, Inc.
5500 Corporate Drive, Pittsburgh, PA 15237

References: 1.Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stress associated with worse outcome? *Anesthesiology.* 1987;67:A1. Abstract. 2. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. *Anesthesiology.* 1986;65:A516. Abstract. 3. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. *Anesthesiology.* 1982;56:112-118. 4. Flacke JW, Bloor BC, Kripke BJ, et al: Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: A double-blind study. *Anesth Analg* 1985;64:897-910. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. *Anesthesiology.* 1987;66:130-135.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia	Dermatological: itching, erythema
Gastrointestinal: nausea, vomiting	Central Nervous System: chills
Respiratory: apnea, postoperative respiratory depression, bronchospasm	Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely.

Protect from light. Store at room temperature 15°-30° C (59°-86° F).

March 1986, March 1987
U.S Patent No. 3,998,834
7518505-M

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Editorial

Standards for Halothane/Caffeine Contracture Test

Henry Rosenberg, MD

Clinicians who have followed the development of diagnostic tests for malignant hyperthermia (MH) over the past score of years may very well feel a sense of confusion and insecurity as to the most accurate laboratory diagnostic test for susceptibility to MH.

In 1970, when Kalow et al. (1) showed that skeletal muscle from patients with MH susceptibility demonstrated an enhanced response to caffeine and to caffeine in the presence of halothane, and then Ellis et al. (2) found that the muscle from MH susceptibles displayed an enhanced contracture response to halothane alone, it all seemed clear. Though inconvenient and invasive, a diagnostic test for MH was at hand.

However, from the outset, certain problems were appreciated. The test is a biological one and many variations in the testing procedure were possible. For example: What should be the ideal halothane concentration for exposure of the muscle? Indeed, what anesthetic is the ideal one? How long should the muscle be exposed to the pharmacologic agent? What is the ideal muscle to use? Is there a difference in contracture response between different muscle groups? What solution? What temperature? How long after an episode of MH should the biopsy be delayed?

In 1977, at the Second International Symposium on Malignant Hyperthermia, and at subsequent workshops, certain guidelines for the contracture test for MH were outlined, such as: the muscle should be stimulated electrically to produce a twitch response; the best temperature for testing was 37°C; caffeine exposure should be done in an incremental dose manner. There, however, was no formal setting out of guidelines. As a result, we soon heard that there were differences among centers. For example, in the interpretation of caffeine and halothane contractures, some believed that the response to caffeine in the presence of halothane was diagnostic for MH susceptibility. Others believed that the test was overly sensitive and not specific enough. When only four or five laboratories in North America were doing such biopsies and each center had its own standards, the problem was not acute. However, as time passed, more and more diagnostic centers began to appear throughout the world and it became obvious that guidelines were needed.

Another reason for standardization was the appearance of noninvasive diagnostic tests for MH. For those tests to be verified, it was necessary that they be correlated with an agreed on diagnostic test that was reproducible in different laboratories. Until recently, noninvasive tests have proved to be of no value in diagnosing MH. However, it took many years to reach that conclusion. The reason, in part, for the delay was the inability to compare the proposed test to an agreed on "gold" standard.

Reacting to these problems, European investigators performing MH susceptibility testing by the halothane/caffeine contracture test met and produced a set of standards for diagnosis (3). They have continued annual discussions of the results of muscle biopsy testing and the interpretation of those results. Nevertheless, "equivocal" results remain.

For all these reasons, it seemed that the time had come for those performing muscle biopsies in North America to agree on standards for the diagnostic test. Accordingly, with the help and support of the Malignant Hyperthermia Association of the United States and the Malignant Hyperthermia Association of Canada, a Biopsy Standards Conference was held at Lake Bluff, Illinois in November 1987. Those actively performing muscle biopsies and those contemplating the

performance of muscle biopsies in both countries attended. There were 24 centers represented in all.

The results of that conference are published in this issue of *Anesthesia and Analgesia* (4).

The biopsy centers agreed on certain protocols in the testing for MH that all should follow. In this way, it was hoped that the data between centers could be interchanged without problems. The temperature of bathing solutions, stimulation parameters, biopsy site, muscle handling and preparation, concentrations of halothane for exposure, and concentrations of caffeine and many other details were all determined.

However, because there were some variations among individual laboratories as to the definition of a normal response and an MH response, it was also agreed that each laboratory should perform 30 biopsies on patients who were considered free of MH susceptibility. Until such time as all centers were performing the test in a similar fashion and controls were collected, it was agreed that a range of normal values should be defined that accorded with observations made to date by biopsy centers. For that reason, a positive caffeine contracture test is defined as either the development of a >0.2 g tension at 2 mM caffeine *or* a caffeine specific concentration of <4 mM caffeine *or* a contracture tension at 2 mM caffeine >7% of the contracture at 32 mM caffeine. The centers will meet again in November 1989 to compare data and actual case histories. We should then be able to define thresholds more precisely.

But, who will collate and keep track of the data? Would there be a central repository for the data? Fortunately, at about the same time, a group of investigators had developed the concept of an MH Registry. The Registry's function is to record data about MH episodes and to serve as an information source for patients and physicians regarding a specific individual's MH susceptibility and its significance to other family members. It was also agreed that the Registry would serve as the data repository for MH testing results. The Registry is located at Hershey Medical Center and it is overseen by Dr. Marilyn Larach. Dr. Gerald Gronert is the Chairman of the Board of the MH Registry.

There are now approximately 20 centers in North America performing muscle biopsies. All have agreed to abide by the standardization protocol so that very soon we hope to have clearly defined standards for MH susceptibility and at last define the sensitivity and specificity of the contracture test.

Nevertheless, questions will remain that need

long-term consideration, such as: Should there be inspection of biopsy centers to ensure that the standards are being adhered to? Is there a minimal number of biopsies that should be done before a center is recognized as a diagnostic center? How will the results of the biopsy standards of North America compare with those of Europe? How can we obtain pure controls? That is, patients who are *guaranteed* not to be MH susceptible and guaranteed not to have other disorders. For example, we frequently obtain control biopsies from patients having prosthetic hip surgery. These individuals may have had trauma to the muscle or muscle hypertrophy or atrophy because of their orthopedic problem. How do we prove prospectively that an MH positive in the laboratory is truly positive? Clearly, a biologic test is not an ideal medical diagnostic test.

We have now come to one station along the road to creation of a sophisticated, reproducible test for MH. Eventually, it is hoped that chromosomal analyses or DNA linkage markers may be developed that will define MH susceptibility. However, we need to know more about the biochemistry and genetics of MH before this can be done. Such is the nature of our understanding of MH.

Although it is clearly recognized that MH is a disorder of skeletal muscle that has certain similarities to other more well-known muscle diseases, MH is still looked on by those outside the specialty of anesthesiology as a peculiar syndrome that has little relevance to those practicing primary care medicine, or perhaps irrelevant to the larger problem of neuromuscular disorders. It is hoped that the demonstration of cooperation and scientific interchange will advance the credibility of the laboratory diagnosis of MH and, in the long run, lead to a better understanding of this dreaded disorder.

References

1. Kalow W, Britt BA, Terreau ME, Haist C. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. Lancet 1970;2:895-8.

2. Ellis FR, Harriman DGF, Kenney NP, Kyei-Mensah K, Tyrrell JH. Halothane-induced muscle contracture as a cause of hyperpyrexia. Br J Anaesth 1971;43:721-2.

3. European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia susceptibility. Br J Anaesth 1984;56:1267-9.

4. Larach MG for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. Anesth Analg 1989;69:511-5.

Hemodynamic Changes and Oxygen Consumption in Burned Patients during Enflurane or Isoflurane Anesthesia

Sergio Gregoretti, MD, Simon Gelman, MD, PhD, Alan Dimick, MD, and Edwin L. Bradley Jr, PhD

GREGORETTI S, GELMAN S, DIMICK A, BRADLEY EL Jr. Hemodynamic changes and oxygen consumption in burned patients during enflurane or isoflurane anesthesia. Anesth Analg 1989;69:431-6.

The effects of enflurane or isoflurane anesthesia on the systemic circulation and whole-body oxygen (O_2) uptake ($\dot{V}o_2$) of 15 burn patients undergoing wound excision and skin grafting procedures were studied. The possibility that burn wound excision might adversely affect pulmonary circulation was also investigated. The patients were preanesthetically in a hyperdynamic-hypermetabolic state, characterized by a resting cardiac index (CI) of 6.2 ± 0.9 $L \cdot min^{-1} \cdot m^{-2}$ (mean ± SD), a $\dot{V}o_2$ (calculated using the Fick principle) of 213 ± 44 $mL \cdot min^{-1} \cdot m^{-2}$, a normal mean systemic arterial pressure (MAP) (92 ± 15 mm Hg), and markedly decreased systemic vascular resistance (SVR) (570 ± 162 $dynes \cdot sec \cdot cm^{-5}$). Mean pulmonary arterial pressure (MPAP) preanesthetically was slightly increased (21 ± 3 mm Hg), while pulmonary vascular resistance (PVR) was in the low-normal range (59 ± 16 $dynes \cdot sec \cdot cm^{-5}$). No difference among the effects of enflurane and isoflurane on systemic and pulmonary hemodynamics and metabolic rate was detected. Induction of anesthesia was associated with a decrease in $\dot{V}o_2$, CI, MAP, and MPAP (P < 0.001), while SVR and PVR did not change. The decrease in CI paralleled the decrease in $\dot{V}o_2$, thereby maintaining whole-body O_2 supply-demand balance. $\dot{V}o_2$ decreased most likely because of lessened tissue O_2 requirements. When anesthesia was discontinued, all metabolic and hemodynamic variables promptly returned to preanesthetic values. No effect of burn wound excision on pulmonary circulation was detected.

Key Words: ANESTHETICS, VOLATILE—enflurane, isoflurane. COMPLICATIONS, BURNS.

Burned patients, after resuscitation from the initial shock phase, develop a hypermetabolic and hyperdynamic state, characterized by marked increases in oxygen (O_2) consumption and cardiac output (1). This state is fully manifested a few days after the injury and persists for several weeks, gradually receding to normal when the wound healing is well underway (2). Patients with large burns need repeated anesthetics during their hospitalization. Enflurane and isoflurane are probably the most commonly used volatile agents. In normal subjects these anesthetics are cardiovascular depressants, but they reduce cardiac output (CO) in a way roughly proportional to whole-body O_2 uptake, so that the balance between O_2 supply and uptake is maintained (3,4). Apparently, no data regarding the effects of inhalation anesthetics on hemodynamic function, metabolic rate, and whole-body O_2 supply-demand balance in burned patients are available.

Animal studies suggest burn wound excision might be associated with pulmonary vasoconstriction, perhaps due to vasoactive substances released from the burn tissues during surgical manipulations (5,6). Pulmonary vasoconstriction may have a significant hemodynamic impact on burned patients in whom the right ventricle, already subjected to an increased flow load because of the increased CO, might poorly tolerate the additional pressure load. The effects of burn wound excision on pulmonary hemodynamics in patients are unknown.

The aims of this study were twofold: to elucidate and compare the effects of enflurane and isoflurane on the circulatory dynamics and O_2 uptake in pa-

Table 1. Patient Characteristics (mean ± SD, n = 15)

Age (yr)	Weight (kg)	BSA* (m²)	Total Burn Size†	Size of 3rd Degree Burn† (% BSA)	Days Since Burn
34 ± 10	80 ± 13	2.0 ± 0.2	51 ± 12	26 ± 12	14 ± 13

*Body surface area.
†Size of burn at admission.

tients with major burns, and to examine the immediate effects of burn wound excision on the pulmonary circulation.

Material and Methods

After Institutional Review Board approval and written informed consents were obtained, 15 patients with second and third degree burns involving more than 35% of the body surface area (BSA) undergoing debridement and skin-grafting procedures under general anesthesia were studied. Three patients were female and 12 male. All patients were without significant cardiac, pulmonary, hepatic, or kidney dysfunction and were not septic at the time of the study. Patient characteristics are summarized in Table 1. Eight of our patients were anesthetized with enflurane (EN group), seven with isoflurane (IS group). In each group there were nine observations, because one patient in the EN group and two patients in the IS group were studied twice, on two different occasions, 24, 2 and 14 days apart, respectively. After insertion of pulmonary and systemic arterial catheters under local anesthesia and intravenous sedation with fentanyl, 0.1–0.2 mg, and diazepam, 5 mg, anesthesia was induced with sodium thiopental, 4–6 mg/kg, followed by vecuronium, 0.1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide (N_2O) in O_2 and enflurane or isoflurane at an end-tidal concentration of 0.7 MAC, continuously measured by a Perkin-Elmer mass spectrometer. Published enflurane and isoflurane MAC values for healthy middle-aged adults (7,8) were used to calculate desired end-tidal concentrations. These relatively low concentrations (approximately 1.2% enflurane and 0.8% isoflurane) were chosen because they had been found in a pilot study to be the highest concentrations usually tolerated by these critically ill patients without causing unacceptable hypotension. To achieve a surgical depth of anesthesia, 60% N_2O was added, aiming at a total anesthetic potency of 1.3 MAC. Ventilation was controlled to maintain arterial Pco_2 levels within normal limits. Ringer's lactated solution and blood were administered throughout the study as needed to maintain pulmonary artery

wedge pressure (PAWP) within 6–15 mm Hg and hemoglobin concentration (Hb) at approximately 10 g/dL. Hemodynamic measurements included heart rate (HR), cardiac output (CO) measured in triplicate by thermodilution, mean systemic arterial pressure (MAP), systolic, diastolic, and mean pulmonary pressures (PASP, PADP, MPAP, respectively), PAWP, and right atrial pressure (RAP). All pressures were measured at end-expiration. Blood temperature, measured by the thermistor at the tip of the pulmonary artery catheter, was assumed as body temperature. The measurements were taken at the following stages: before induction of anesthesia, while the dressings were still in place and at an ambient temperature of 24°C (baseline, Stage 1); 30–45 min after induction of anesthesia, when the desired end-tidal concentration of the appropriate anesthetic had been kept constant for at least 15 min, but before surgery began (Stage 2); at the end of surgery but with the patients still anesthetized (Stage 3); in the recovery room 1.5 to 3 hr after anesthesia, when the patients were hemodynamically stable, were breathing O_2-enriched air through a face mask, were not shivering with body temperature within ±0.2°C of baseline values, and had been given morphine to obtain pain relief (Stage 4).

Arterial and mixed venous blood samples were drawn during the hemodynamic measurements and pH, Pco_2, Po_2, Hb, oxygen saturation, and contents were determined using an IL 1303 Blood Gas Analyzer and IL 282 Cooximeter (Instrumentation Laboratory, Lexington, MA). The following variables were derived using standard formulae: cardiac index (CI), stroke volume index (SVI), and systemic and pulmonary vascular resistance (SVR, PVR). Whole-body O_2 consumption ($\dot{V}o_2$) was calculated as CI times arteriovenous O_2 content difference ($AVDo_2$). Oxygen extraction ratio (o_2ER) was calculated as $AVDo_2$ times 100 divided by arterial blood O_2 content.

The data were summarized as mean ± 1 SD. Comparisons between groups were performed using a χ^2 analysis (for categorical variables) and the two-sample t-test (for continuous variables). Comparisons among stages for each group were made using repeated measures analysis of variance. Fisher's pro-

Table 2. Hemodynamic and Metabolic Variables in Burned Patients during Inhalation Anesthesia (mean ± SD, n = 18)

Variable	Units	Stage 1 (baseline)	Stage 2	Stage 3	Stage 4
HR	beats/min	123 ± 13	107 ± 13‡	101 ± 12‡	127 ± 16
MAP	mm Hg	92 ± 15	66 ± 10‡	68 ± 10‡	87 ± 16
CL	$L \cdot min^{-1} \cdot m^{-2}$	6.2 ± 0.9	4.3 ± 0.8‡	4.4 ± 0.8‡	6.6 ± 1.1
SVI	$mL \cdot beat^{-1} \cdot m^{-2}$	49.8 ± 9.2	40.1 ± 7.1‡	44.1 ± 8.4*	52.3 ± 8.8
SVR	$dynes \cdot sec \cdot cm^{-5}$	570 ± 162	565 ± 136	577 ± 185	510 ± 132
PAWP	mm Hg	11.7 ± 3.0	9.7 ± 2.6	10.2 ± 2.2	11.7 ± 2.9
RAP	mm Hg	8.2 ± 2.9	8.3 ± 3.1	8.8 ± 2.5	7.7 ± 2.9
PASP	mm Hg	32.4 ± 6.2	26.1 ± 4.1‡	28.2 ± 3.4†	30.1 ± 4.9
PADP	mm Hg	13.6 ± 2.8	10.9 ± 5.5†	11.4 ± 2.6*	13.8 ± 2.9
MPAP	mm Hg	20.6 ± 3.1	16.2 ± 3.0‡	17.2 ± 2.7‡	19.7 ± 2.7
PVR	$dynes \cdot sec \cdot cm^{-5}$	59 ± 16	64 ± 22	67 ± 20	50 ± 12
AVDo$_2$	mL/dL	3.5 ± 0.5	2.8 ± 0.4‡	2.5 ± 0.6‡	3.6 ± 0.7
Vo$_2$	$mL \cdot min^{-1} \cdot m^{-2}$	213 ± 44	117 ± 20	110 ± 20	233 ± 56
Sv̄o$_2$	%	70.7 ± 5.7	77.9 ± 4.5‡	79.3 ± 5.0†	71.9 ± 6.2
o$_2$ER	%	25.8 ± 4.4	21.4 ± 4.6†	20.3 ± 4.8‡	26.5 ± 5.5
Temp	°C	37.6 ± 0.8	36.5 ± 0.8‡	34.4 ± 1.2‡§	37.6 ± 0.7

See text for abbreviations.
*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ Stages 2, 3, and 4 vs Stage 1.
§$P < 0.001$ Stage 3 vs Stage 2.

tected least significant difference test was used for comparing Stage 1 (baseline) against Stages 2–4 and for comparing Stages 2 and 3. Pearson's correlations between variables were calculated combining the data points from the four stages. Comparisons among correlations were performed by transforming the correlations to Fisher's z and using a χ^2 statistics (9). A value of $P < 0.05$ was accepted as statistically significant.

Results

Patients anesthetized with enflurane or isoflurane were similar in age, weight, size of burns, postburn day of study, and duration of surgery (155 ± 45 and 180 ± 38 min in EN and IS group, respectively). Throughout the study, only two variables were different between the groups in a statistically significant way: baseline mixed venous O$_2$ saturation (Sv̄o$_2$) in the EN group was 74 ± 4.8% and 68 ± 5.1% in the IS group ($P < 0.05$); at Stage 4 AVDo$_2$ in the EN group was 3.4 ± 0.6 and 3.9 ± 0.7 mL/dL in the IS group ($P < 0.02$). Since the differences between the groups were of negligible clinical relevance, the results from all 15 patients were combined and presented in Table 2.

Anesthesia induction was associated with significant decreases in HR, SVI, CI, MAP, and MPAP, while SVR and PVR did not change. The decrease in CI was unrelated to changes in PAWP or RAP. The latter pressures were maintained close to baseline by administration of fluids and bloods according to the study protocol.

Statistically significant correlations were found between MPAP and CI ($r = 0.51$, $P = 0.0001$) and between PVR and CI ($r = -0.40$, $P = 0.0005$). No effect of the wound excision on pulmonary vasculature was detected, since no change in PVR occurred in the postoperative stages. Throughout the study PADP and PAWP correlated well ($r = 0.83$, $P = 0.0001$) and the PADP-PAWP difference ranged from 0 to 5 mm Hg.

A marked decrease in V̇o$_2$ occurred during anesthesia, a decrease proportionally greater than the concomitant decrease in CI. In fact, V̇o$_2$ and CI decreased to approximately 55% and 70%, respectively, of baseline values. As a consequence of a decrease in O$_2$ supply less than the decrease in O$_2$ consumption, AVDo$_2$ and o$_2$ER decreased, while Sv̄o$_2$ increased. A strong correlation between CI and V̇o$_2$ was found ($r = 0.80$, $P = 0.0001$).

Arterial pH and Paco$_2$ remained within normal limits throughout the study period. Baseline Pao$_2$ while breathing room air averaged 73 ± 11 mm Hg and was consistently greater than 100 mm Hg during the following stages. Preoperative Hb was 10.6 ± 1.3 g/dL and did not change during the study. When anesthesia was discontinued, all hemodynamic and metabolic variables rapidly returned to baseline values.

Discussion

Baseline hemodynamic and metabolic profiles of our patients were comparable with those reported in other series (1). All patients were in a hyperdynamic-hypermetabolic state with resting CI and V̇o$_2$ well

above normal values, which for this age group would average 3 $L \cdot min^{-1} \cdot m^{-2}$ and 130 $mL \cdot min^{-1} \cdot m^{-2}$, respectively (10). Although $\dot{V}o_2$ was increased, $AVDo_2$ was 30% less than normal, and $S\bar{v}_{O_2}$ and o_2ER, which reflect the adequacy of the whole-body O_2 supply-demand balance (11), were within normal limits.

Systemic Hemodynamics

A large decrease of CI was observed in our patients during enflurane or isoflurane administration, while, in contrast, these anesthetics only slightly depress CI in subjects with normal hemodynamics (3,4). Decreases in stroke volume in our patients and in normal subjects were similar. While in normal subjects the decrease in stroke volume associated with enflurane and isoflurane is offset by an increase in HR, in our burn patients the decrease in stroke volume was associated with a decrease in HR, thus explaining the large decrease in CI. A decrease in HR has been reported following enflurane or isoflurane administration in subjects premedicated with morphine (12). The decrease in HR observed after induction of anesthesia in our study might therefore be explained by the 0.1–0.2 mg fentanyl, administered when the intravascular catheters were placed. However, the role of fentanyl in determining the decrease in HR was probably negligible, since the measurements were made when the effects of such a dose would have already dissipated.

The increased CO in burned patients is mainly a consequence of the increase in $\dot{V}o_2$ (1). Since in our study enflurane and isoflurane simultaneously decreased both $\dot{V}o_2$ and CO, it is possible that CO decreased because of lessened tissue metabolic requirements rather than direct cardiac effects of the anesthetics. The strong correlation between CI and $\dot{V}o_2$ found in our study, although it does not prove a causally linked relationship between the variables, supports this hypothesis. Since an increase in HR is the main mechanism used by burned patients to increase CO, this sequence of events, i.e., decreased $\dot{V}o_2$ and hence CO, may well explain the decrease in HR observed during anesthesia.

The increased CO in burned patients was associated with decreased SVR, which did not change during anesthesia, although enflurane and isoflurane consistently decreased SVR in normal subjects (3,4). This decrease in SVR apparently resulted from vasodilation in discrete vascular beds rather than a generalized vasodilation, since in burned patients the perfusion of the liver, burn wound, and probably heart and respiratory muscles is increased, while

kidney, uninjured skin, and limb muscles are normoperfused (13). During anesthesia, the vascular resistance in each of the different components of the systemic vascular bed may increase, decrease, or remain unchanged as the result of the interaction of a host of factors. We suspect that the lack of effects of the anesthetics on SVR in burned patients was due to the fact that changes in resistance in one area offset the changes in other areas.

Oxygen Consumption

In this study, whole body $\dot{V}o_2$ markedly decreased during anesthesia most likely because of decreased tissue metabolic requirements, as no evidence of tissue hypoperfusion or metabolic acidosis was detected. In addition, a decrease in $\dot{V}o_2$ due to an inadequate CO is associated with increases in $AVDo_2$ and o_2ER, and a decrease in $S\bar{v}_{O_2}$ (11), the opposite of our findings. The decrease in $\dot{V}c_2$ in our patients was apparently induced by the anesthetics (3,4) in combination with mechanical ventilation (14,15), and not by the decrease in body temperature, because $\dot{V}o_2$ decreased 45% immediately following induction of anesthesia, at a time when body temperature had decreased only 1.2°C. Although the effect of temperature on metabolic rate in burned patients is unknown, it is unlikely that this small decrease in temperature resulted in such a large decrease in $\dot{V}o_2$; in normal anesthetized subjects, a 1°C decrease in body temperature is followed by only a 5%–7% decrease in metabolic rate (16). In addition, when anesthesia was discontinued, $\dot{V}o_2$ promptly returned to preanesthesia value regardless of body temperature at that point.

Mechanical ventilation also contributes to the decrease in $\dot{V}o_2$ during anesthesia, probably by decreasing the work and hence the O_2 consumption of the respiratory muscles (14,15). The O_2 consumption of respiratory muscles increases with minute ventilation (17). In normal subjects the O_2 cost of breathing amounts to 0.5–1 mL of O_2 consumed by the respiratory muscles per liter of minute ventilation (17). In burned patients ventilation is universally increased to meet the increased O_2 requirements (18). The estimated resting minute ventilation in our patients, with a 50% BSA burn, was approximately 10 L/min (19). The oxygen cost of breathing in burn patients apparently has not been reported. However, in absence of overt lung pathology (e.g., inhalation injury, pneumonia, atelectasis), it is probably close to normal, since lung resistance and compliance, the major determinants of work of breathing, are usually unaf-

fected by a cutaneous burn alone (18). If our assumption is correct, in our patients, in whom clinical and radiological examination of the lungs were within normal limits, the O_2 cost of breathing was about 10 mL O_2/min. Mechanical ventilation, therefore, contributed a mere 5% of the overall decrease in $\dot{V}o_2$ during anesthesia.

Marked decreases in $\dot{V}o_2$ and in urinary catecholamine output have been reported by Taylor et al. following morphine administered in a dose of approximately 0.75 mg/kg to burned patients (20). Since the metabolic response to thermal injury is due to an increased sympatho-adrenergic activity mediated by the central nervous system (CNS), the authors concluded that morphine was able to reduce the metabolic response to injury by depressing the CNS and therefore decreasing the CNS-mediated adrenergic activation. We speculate that enflurane and isoflurane decrease the metabolic rate in burned patients by a similar mechanism. In addition, enflurane, besides inhibiting the sympathetic system at the central level, may depress catecholamine release by a direct inhibition of the adrenal medulla (21). In contrast, $\dot{V}o_2$ did not change in burned patients following administration of ketamine (22), which is well known to stimulate the sympathetic system (23) and therefore is unlikely to modify the enhanced sympathetic discharge in these patients.

Pulmonary Hemodynamics

Baseline pulmonary circulation in our patients was characterized by slightly elevated pressures associated with low-to-normal vascular resistance, while CO and hence pulmonary blood flow were two times greater than normal. Pulmonary pressures, however, were in the normal range when CO decreased during anesthesia. Therefore, baseline MPAP increased because of an increase in pulmonary blood flow rather than an increase in pulmonary vascular tone. Since in the normal lung an increased CO is associated with increased MPAP and decreased PVR (24), the correlations between MPAP and CI, and PVR and CI, in our patients were compared with similar correlations calculated using data obtained in healthy volunteers during exercise (25). The correlations were not statistically different in normal and burned patients, indicating that the pulmonary circulation in our patients was able to respond in a normal fashion to changes in flow. Pulmonary vasoconstriction is not a feature of the burn injury per se and increased pulmonary vascular resistance in burn patients should probably be regarded as a manifestation of other disease processes; e.g., smoke inhalation or sepsis (26,27).

No effects of burn wound excision on pulmonary circulation were detected. Our results contrast with the increase in pulmonary pressure observed in an animal model (5,6). The contrast can be in part explained by a different reactivity of pulmonary circulation in humans and animals, and also by differences in study design. In addition, only one-third of the animals studied had significant lung dysfunction following wound excision (5,6). It appears that the animals in these studies that developed lung abnormalities were likely to be septic, and, therefore, the observed pulmonary vascular changes could have resulted from the septic process rather than the wound excision itself.

In conclusion, this study has shown that enflurane and isoflurane decrease $\dot{V}o_2$ and CO in hypermetabolic-hyperdynamic burned patients. The effects of the two anesthetics on the cardiovascular system and metabolic rate were virtually identical. The decrease in CO paralleled the decrease in $\dot{V}o_2$, thereby maintaining the O_2 supply-demand balance. Pulmonary hemodynamics in the burned patients were characterized by slight increases in MPAP resulting from an increased CO, since PVR was normal. Burn wound excision did not affect pulmonary circulation.

References

1. Gump FE, Price JB, Kinney JM. Blood flow and oxygen consumption in patients with severe burns. Surg Gynecol Obstet 1970;130:23-8.
2. Cope O, Nardi GL, Quijano M, et al. Metabolic rate and thyroid function following acute thermal trauma in man. Ann Surg 1953;157:165-74.
3. Calverley RK, Smith NT, Prys-Roberts C, et al. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 1978;57:619-28.
4. Dolan WM, Stevens WC, Eger EJ, et al. The cardiovascular and respiratory effects of isoflurane-nitrous oxide anaesthesia. Can Anaesth Soc J 1974;21:557-68.
5. Demling RH, Katz A, Lalonde C. The effects of immediate vs delayed burn wound excision on pulmonary function. J Crit Care 1986;1:154-72.
6. Demling RH, Katz A, Lalonde C, et al. The immediate effect of burn wound excision on pulmonary function in sheep: the role of prostanoids, oxygen radicals, and chemoattractans. Surgery 1987;101:44-55.
7. Gion H, Saidman LJ. The minimum alveolar concentration of enflurane in man. Anesthesiology 1971;35:361-4.
8. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 1975;42:197-200.
9. Ostle B, Mensing RW. Statistics in Research, 3rd ed. Ames, Iowa: Iowa State University Press, 1975:240-2.
10. Bell GH, Emslie-Smith D, Patterson CR. Textbook of Physiology, 10th ed., New York: Churchill Livingstone, 1980:12-8.
11. Snyder JV. Assessment of systemic oxygen transport. In: Oxygen Transport in the Critically Ill. Snyder JV and Pinsky MR, eds. Chicago: Year Book Medical Publishers, 1987:179-98.

12. Eger EJ. The pharmacology of isoflurane. Br J Anaesth 1984; 56:71S–99S.

13. Aulick LH, Goodwin CW, Becker RA, Wilmore DW. Visceral blood flow following thermal injury. Ann Surg 1980;193:112–6.

14. Brismar B, Hedenstierna G, Lundh R, Tokics L. Oxygen uptake, plasma catecholamines and cardiac output during neurolept-nitrous oxide and halothane anesthesia. Acta Anaesthesiol Scand 1982;26:541–9.

15. Christensen KJ, Andersen AP, Jorgensen S. Energy expenditure on breathing during anaesthesia. Acta Anaesthesiol Scand 1985;29:280–2.

16. Michenfelder JD, Uihlein A, Daw EF, Theye RA. Moderate hypothermia in man: haemodynamic and metabolic effects. Br J Anaesth 1965;37:738–45.

17. Nunn JF. Applied respiratory physiology, 3rd ed. London: Butterworth & Co, 1987:104–6.

18. Artz CP, Moncrief JA, Pruitt BA. Burns. A Team Approach. Philadelphia: Saunders Co, 1979:37.

19. Nishimura N, Hiranuma N. Respiratory changes after major burn injury. Crit Care Med 1982;10:25–28.

20. Taylor JW, Hander EW, Skreen R, Wilmore DW. The effects of central nervous system narcosis on the sympathetic response to stress. J Surg Res 1976;20:313–20.

21. Göthert M, Wendt J. Inhibition of adrenal medullary catecholamine secretion by enflurane. 1. Investigation in vivo. Anesthesiology 1977;46:400–3.

22. Gooding JM, Dimick AR, Tavakoli M, Corssen G. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients. Anesth Analg 1977;56:813–6.

23. Corssen G, Reves JG, Stanley TH. Intravenous anesthesia and analgesia. Philadelphia: Lea E. Febinger, 1988:99–173.

24. Murray JF. The Normal Lung, 2nd ed. Philadelphia: WB Saunders Co, 1986:152–4.

25. Holmgren A, Jonsson B, Sjöstrand T. Circulatory data in normal subjects at rest and during exercise in recumbent position, with special reference to the stroke volume at different work intensities. Acta Physiol Scand 1960;49:343–63.

26. Martyn JA, Snider MT, Sayfelbein SK, et al. Right ventricular dysfunction in acute thermal injury. Ann Surg 1980;191:330–5.

27. Clowes GH, Hirsch E, Williams, et al. Septic lung and shock lung in man. Ann Surg 1975;181:681–92.

Malignant Hyperthermia in Humans—Standardization of Contracture Testing Protocol

Agnes T. Melton, BS, Richard W. Martucci, MA, Nguyen D. Kien, PhD, and Gerald A. Gronert, MD

Malignant hyperthermia (MH) diagnostic biopsy centers across North America have not previously been standardized in regard to protocols and specific muscles. Recent standardization criteria prompted this study of the vastus and rectus abdominis muscles. This study evaluated changes in contracture tension after electrical stimulation of 271 bundles taken from the vastus (n = 16) and rectus abdominus (n = 19) muscle biopsies of normal individuals when exposed to tissue baths in the absence of and in the presence of caffeine (0.5, 1.0, 2.0, 4.0, 8.0, and 32.0 mM) alone, halothane (1% or 3%) alone, or the combination of halothane (1%) plus caffeine (0.25, 0.5, 1.0, 2.0, 4.0, and 32.0). Caffeine threshold concentration was that concentration of caffeine that produced a 7% increase in tension. Caffeine specific concentration (CSC) and halothane caffeine specific concentration (HCSC) were those concentrations of caffeine alone or of halothane plus caffeine that produced a 1 g increase in tension. The concentration of caffeine alone that increased the contracture tension by 7% averaged 6.7 ± 0.3 mM for vastus, significantly >4.1 ± 0.2 mM for the rectus muscle biopsies. Caffeine specific concentration was significantly greater for vastus muscle (7.7 ± 0.7 mM) than it was for rectus muscle (4.9 ± 0.4 mM). Three percent halothane alone showed contractures in 3/41 vastus (all <0.5 g) and 18/54 rectus muscle bundles (8 >0.5 g). Mean HCSC was statistically significantly greater for vastus muscle (1.9 ± 0.2 mM) than for rectus muscle (1.2 ± 0.2 mM). Vastus had significantly higher thresholds and more consistent results than rectus; rectus responses frequently suggested malignant hyperthermia susceptibility in control patients. Comparison of present findings to those of diagnostic vastus biopsies suggests that caffeine alone testing complements halothane alone and that 3% halothane yields more accurate results than 2% halothane for diagnosing susceptibility.

Key Words: HYPERTHERMIA, MALIGNANT.

One of the intriguing aspects in the diagnosis of susceptibility to malignant hyperthermia (MH) is that the tissue (and the susceptible individual) appears normal until stressed. To diagnose susceptibility, one must quantitate a lower than normal threshold to stimuli such as heat, anesthetics, and various drugs that produce muscle contractures or increased metabolism. Thus far, in vitro contracture testing of biopsied muscle with caffeine alone or halothane alone yields the most reliable thresholds (1), defined as the concentration of drug at which a specified increase in muscle tension occurs. Malignant hyperthermia testing in North America has been complicated by the fact that many laboratories use slightly different testing protocols and even different muscle, e.g., vastus or rectus abdominis. Such differences yield inconsistencies when attempting to compare results between various laboratories. These problems are now being addressed by standardizing the protocol and the muscle, as defined by the North American MH Registry (Table 1). This protocol is based on the recent encouraging findings from European centers, which demonstrate that standardization enhances reproducibility and precision (1). The purpose of this study was to reexamine contracture responses of normal muscle to caffeine or halothane, or both, using the proposed standardized protocol (Table 1).

The study examined contracture results of biopsies taken from the vastus and rectus abdominis muscles, exposed in tissue baths to caffeine alone, halothane
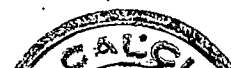
Table 1. Recommendations for Standardization of the
Caffeine Halothane Contracture Test*

An abnormal contracture response or a positive malignant
 hyperthermia muscle biopsy is defined as follows.

Accepted Criteria:
 A positive halothane contracture test is defined as a
 >0.2–0.7 g contracture after exposure to 3% halothane for 10
 min. The exact value of this range of abnormal shall be
 determined by each testing laboratory after the evaluation of at
 least 30 normal control muscle biopsies.

 A positive caffeine contracture test is defined as the
 observation of either: 1) the development of ≥0.2 g tension at
 2 mM caffeine; or 2) a caffeine specific concentration (CSC) at
 <4 mM caffeine; or 3) the percent of maximal tension is >7%
 change above the baseline at 2 mM caffeine.

Controversial Criterion:
 (A positive halothane caffeine contracture test is defined as the
 development of a 1 g contracture after exposure to a
 concentration of ≤1 mM caffeine in the presence of 1%
 halothane.)

*Modified from Ref. 13.

alone, and halothane plus caffeine. In addition, we
compared contracture thresholds of control patients
to those of a diagnostic population, to determine
better approaches to differentiation of normal from
susceptible muscle.

Methods and Materials

Biopsies were obtained from 35 patients during re-
gional or general anesthesia while undergoing sur-
gery involving the thigh or abdomen. The protocol
was approved by our Human Subjects Review Com-
mittee, and patients were selected who had appar-
ently normal muscle function and no past or family
history suggestive of MH. The biopsies were from
vastus lateralis (16 patients) or rectus abdominis
muscles (19 patients). The specimens, approximately
3.5 cm × 1.5 cm × 1.5 cm, were transported to the
laboratory at room temperature in Krebs-Ringers so-
lution (mM: Ca:2.5, Na:134, K:4.6, Mg:1.0, Cl:124,
HCO_3:16, H_2PO_4:1.2, SO_4:1.0, and glucose:11.1), dis-
sected into bundles along the long axis of the muscle,
mounted into six parallel tissue baths at 37°C and
bubbled with carbogen (2). The first six bundles were
mounted within 1 hr of excision. Approximate bun-
dle dimensions were 1.5 cm × 0.2 cm × 0.2 cm,
virtually all bundles had weights of 40–120 mg; one
end of the bundle was attached to a transducer (peak
capacity: 50.0 g). Each bundle was electrically stimu-
lated with 2 msec pulses at 0.1 Hz through platinum
field electrodes (4.5 cm × 0.5 cm × ~0.1 cm) with a
model S4 Grass stimulator augmented by a current

booster. If mechanical twitches did not occur with
stimulation, the bundle was discarded. With use of
optimal polarity and supramaximal voltage, a length-
tension curve was determined and the length provid-
ing maximal twitch tension was used for the study
(2). Bundles from each patient were exposed to 1)
caffeine alone; 2) 3% halothane alone; 3) 1% halo-
thane alone and 1% halothane plus caffeine. Only
one test was performed on each bundle. The length
and weight of the bundles were determined after
testing to calculate cross-sectional area:

$$\text{Area (cm}^2) = \frac{\text{weight (g)}}{\text{length (cm)} \times \text{density (g/cm}^3)}.$$

Density of muscle is 1.06 g/cm^3.

Caffeine Alone Testing
(Three Baths Simultaneously)

A 100 mM stock solution of caffeine in 37°C Krebs-
Ringers solution was added to the 14-mL tissue baths
with use of micropipets in increments that provided
the following concentrations: 0.5, 1.0, 2.0, 4.0, 8.0 (if
4.0 mM did not produce a threshold), and 32.0 mM.
The baths were not flushed after caffeine increments,
and at least 4 min (or an additional 2 min beyond the
plateau of a contracture) elapsed between each suc-
cessive caffeine dose. From the resultant recording
and transducer calibrations, grams tension was cal-
culated for each caffeine dose.

Three methods were used to express these values:
1) Fraction of peak tension versus caffeine concentra-
tion: each gram tension value for a specific bundle
was divided by the gram tension at 32 mM caffeine,
yielding the fraction of peak tension value (3). When
graphed, the caffeine concentration corresponding to
a 7% increase in tension over the lowest value was
identified as the threshold (Table 1). 2) Grams tension
versus caffeine concentration: on this graph, the
caffeine concentration corresponding to a 1 g increase
in tension over the lowest value was identified as the
caffeine specific concentration (CSC) (4). 3) Tension in
grams/cm² versus caffeine concentration: each gram
tension value was divided by the cross-sectional area
of the muscle bundle.

Halothane Alone Testing
(Three Baths Simultaneously)

Each bundle was subjected to 3% or 1% halothane
delivered for 10 min through a temperature-compen-
sated vaporizer at a 2-L flow of carbogen with use of
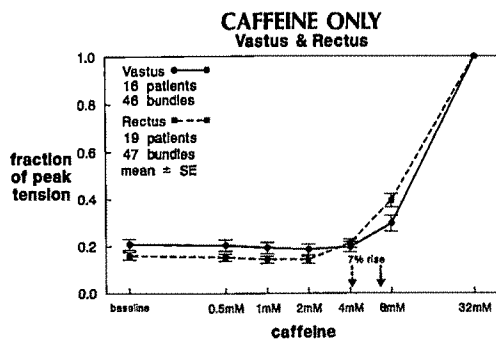
Figure 1. Fraction of peak tension versus caffeine concentration in normal control patients. See text for details.

Figure 2. Grams tension versus caffeine concentration in normal control patients. See text for details.

a roller pump between the vaporizer and the baths. Only a portion of the 2-L flow was directed through the baths; the line was tapped for analysis by a mass spectrometer before reaching the baths. Grams tension and g/cm^2 values quantified responses.

1% Halothane Plus Caffeine Testing (Three Baths Simultaneously)

Bundles were subjected to 1% halothane for 10 min followed by successive doses of caffeine: 0.25, 0.5, 1.0, 2.0, 4.0, and 32.0 mM (using the same method as for caffeine only). Fraction of peak tension, grams, and g/cm^2 were determined. The only defined threshold to date for this test is for the grams tension method and is referred to as the halothane caffeine specific concentration or HCSC (1 g increase from the lowest tension value in the presence of 1% halothane) (4).

Anesthetic management for these patients included volatile agents (enflurane, isoflurane, halothane, and nitrous oxide); muscle relaxants (succinylcholine, pancuronium, metocurine, and vecuronium); opiates (fentanyl, alfentanil, morphine sulfate, and methadone); tranquilizers (droperidol, haloperidol, and midazolam); thiopental; and local anesthetics (lidocaine and bupivacaine).

Results are expressed as mean ± SE and statistical significance was attained when the unpaired Student t-test was $P < 0.01$; χ^2 analysis compared contracture incidences in groups exposed to 3% halothane-alone, $P < 0.01$.

Results

Caffeine Alone

Figures 1 and 2 show dose-response curves for vastus and rectus muscles with use of two different methods of expression: 1) fraction of peak tension; and 2)

grams. Figure 1 illustrates the fraction of peak tension in relation to increasing concentrations of caffeine. The 7% increase in tension (threshold concentration) is 6.7 ± 0.3 mM for vastus and 4.1 ± 0.2 mM for rectus. These values were significantly different. The caffeine concentration at which the 7% increase takes place was never <2 mM, which is the critical level for diagnosis of susceptibility in our laboratory (Table 1).

Figure 2 demonstrates values for grams tension in response to increasing doses of caffeine. The caffeine specific concentration (CSC) is significantly greater for vastus muscle as compared with rectus (7.7 ± 0.7 mM versus 4.9 ± 0.4 mM). Three of 44 vastus and 15 of 50 rectus bundles had CSC values of <4 mM, which is Britt's estimate of the minimal value in normal muscle (4), and one of the proposed Registry standards (Table 1). None of 46 vastus and 4 of 50 rectus bundles had an increase in tension of ≥0.2 g in response to 2 mM caffeine concentration; this is the critical value for the European standards (1). The figures demonstrate that the rectus dose-response curves rise more quickly and their thresholds (7% and CSC) are consequently lower than those of vastus.

Changes in grams tension per cross-sectional area in relation to increases in caffeine concentration are not illustrated. Mean cross-sectional area was 0.037 ± 0.003 cm^2; g/cm^2 values are proportional to values for tension in grams. The threshold was estimated to be between 4 and 8 mM caffeine for both vastus and rectus muscles.

Numerical discrepancies exist between the numbers of muscle bundles on the two figures. The grams tension graphs had more bundles than fraction of peak tension graphs because some muscle bundles ripped before maximal caffeine concentration was attained.

Halothane Alone

3%: results for this test are expressed in grams and g/cm^2. Vastus: Baseline tension was 1.70 ± 0.20 g and
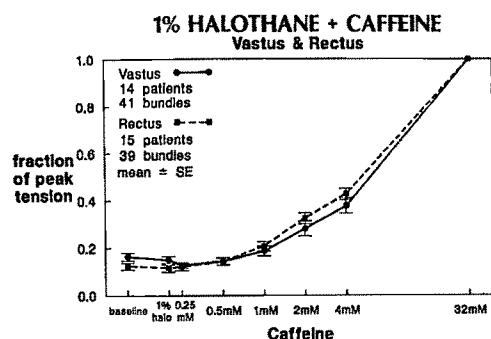
Figure 3. Fraction of peak tension versus 1% halothane-caffeine concentration in normal control patients. See text for details.

Figure 4. Grams tension versus 1% halothane-caffeine concentration in normal control patients. See text for details.

77 ± 14 g/cm^2; tension usually decreased during administration of 3% halothane. Three of 41 bundles developed contractures to 3% halothane: 0.035 (2 bundles) and 0.105 g. *Rectus*: Baseline tension was 1.87 ± 0.14 g and 76 ± 6 g/cm^2; tension decreased in most bundles, but 18 of 54 bundles developed contractures to 3% halothane: 0.10, 0.14, 0.17 (2 bundles), 0.28 (2 bundles), 0.32, 0.34, 0.38, 0.46, 0.52, 0.60 (3 bundles), 0.76, 1.02, 1.28, and 1.70 g. The rectus muscle produced contractures significantly greater in number (x^2 analysis) and magnitude (unpaired *t*-test) than those of vastus. There was one vastus muscle bundle (data not included) that had a contracture of 0.98 g. This muscle was severely damaged during excision; only three of seven bundles had twitches. The histology report confirmed that the specimen was badly damaged physically, and the muscle bundles from this patient were discarded from the study.

1%: baseline vastus tension was 2.23 ± 0.24 g and 77 ± 10 g/cm^2. Three of 44 bundles showed a contracture: 0.04, 0.04, and 0.08 g. Baseline rectus tension was 1.96 ± 0.15 g and 63 ± 8 g/cm^2. Two of 47 bundles developed a contracture: 0.34 and 1.44 g.

1% Halothane Plus Caffeine

Figures 3 and 4 show dose-response curves for vastus and rectus muscle. Figure 3 shows the fraction of peak tension in response to 1% halothane plus increasing doses of caffeine. The slope of the dose-response curve is gradual, making the determination of an exact threshold value difficult. Figure 4 illustrates the mean tension values in grams in response to increasing doses of caffeine. The halothane caffeine specific concentration (HCSC) of 1.9 ± 0.2 mM for the vastus differed significantly from the value of 1.2 ± 0.2 mM for the rectus muscle. The lower limits of HCSC values were 0.60 mM for vastus and 0.22 mM for the rectus, with 11 of 41 vastus bundles and 26 of
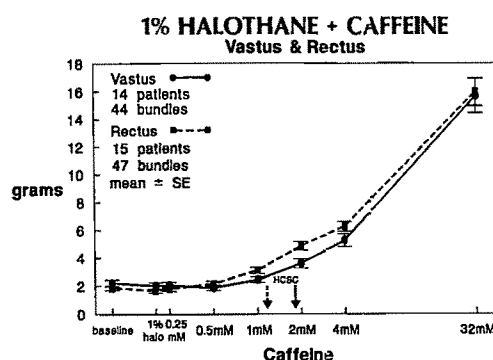
47 rectus bundles showing an HCSC value of <1 mM, which is Britt's critical value for diagnosing susceptibility (4) and one of the proposed Registry standards. For g/cm^2, data not graphed, thresholds were estimated to be 2–4 mM caffeine concentration for vastus and 0.5–1 mM for rectus abdominis muscle.

Histology and Histochemistry

Overt consistent pathology was not observed. There were scattered instances of diffuse, and occasionally, pronounced fiber type atrophy as well as type-grouping patterns. One clinically normal patient had abnormal histopathologic changes: Pyknotic nuclear clumping was seen in the presence of very large and very small muscle fibers. The large fibers showed splitting and many had a central change giving the fibers a target-core like appearance. The contracture results were within our normal ranges.

Discussion

As attempts are made to standardize contracture testing techniques in North America and to compare results from different laboratories, it is vital to agree on methods for expressing the results that are suitable for making such comparisons. Variations among laboratories may exist for mechanical reasons (the actual voltage from the stimulator, the level of functioning of the current boosters, transducers, etc.) and methodologic reasons (timing of drug doses, the specific muscle, thickness of the muscle bundle, and interpretation of contracture data).

Caffeine Alone

The method involving fraction of peak tension (grams tension at each individual caffeine concentration di-

Table 2. Collated Control Data for Caffeine Alone Test

No. of Patients	Muscle	Findings	Reference
Not stated	Rectus abdominis	Threshold: 2–8 mM	Moulds and Denborough (11)
20	Vastus lateralis	CSC: 5.5 ± 0.6 mM*†	Britt et al. (5)
33	Quadriceps	Threshold: 2–4 mM	Gronert (2)
10	Quadriceps	CSC: 7.5 ± 1.1 CSC > 4.1 for all controls	Britt et al. (4)
19	Rectus abdominis	CSC: 4.8 ± 2.1	Nelson et al. (7)
29	Not specified	CSC: 3.5 mM − 10 mM	Brownell et al. (6)
15	Quadriceps	Response to 2 mM caffeine: 0.17 ± 0.05 g CSC: 7.92 ± 1.16 13/15 patients had 0.2 g contractures at 2 mM caffeine	Rosenberg and Reed (8)
20	Vastus medialis	19/20 patients had <0.2 g contracture in response to 2 mM caffeine	Ording and Skovgaard (9)

*CSC = concentration of caffeine eliciting a 1 g contracture; †mean ± SE.

vided by grams tension at maximal caffeine concentration) normalizes the dose-response curves with respect to the variations mentioned previously. With the fraction of peak tension method, the entire dose-response curve is evaluated, thereby providing definitive information about the pattern of the muscle response. The 7% increase in twitch tension appears to identify the threshold of the sigmoidal dose-response curve.

Many researchers (4–10) use individual grams tension values to express results of contracture testing. The CSC (defined as the caffeine concentration corresponding to a 1 g increase over the lowest point on the graph) is a convenient threshold; some (4–6) halt caffeine additions after the CSC is reached and thus do not define an entire dose response curve. Because it does not take into account the maximal tension attained by the muscle bundle, the CSC threshold is affected by the previously mentioned interlaboratory variations. This result makes its use less than ideal for interlaboratory comparisons. Also, the 7% value provided a more consistent lower limit for normal muscle than did the CSC.

With g/cm² on the ordinate, the dose-response curve is normalized with respect to differences in cross-sectional area of the muscle bundles. This result does not provide a consistent threshold, in part because measurements of length and weight are relatively inexact.

Results of caffeine-alone contracture testing of control muscle by other laboratories are summarized in Table 2. In most studies (5–7), the threshold for caffeine was above 2 mM for control muscles. In other studies (1,2,9), small contractures have been observed at 2 mM caffeine concentration, similar to our results. CSC values ranged from 3 to 10 mM and the 7% threshold was in general not specified.

Halothane Alone

Most muscle bundles responded to 3% halothane with a relaxation response. However, there were contracture responses in some individual bundles of both vastus and rectus exposed to 3% halothane. The greatest value of the three vastus bundle contractures was 0.105 g. The rectus muscle bundles developed a greater number and magnitude of contractures in response to 3% halothane (18 of 54 bundles, 8 >0.5 g, highest value 1.70 g).

In response to 1% halothane, the vastus again showed insignificant contractures, whereas two rectus bundles had 0.34 and 1.70 g contractures.

Results from others (11,12) using halothane alone testing showed contracture responses in some control rectus abdominis muscle. Studies (2,10) on control vastus muscle showed no contracture with one exception: 0.02 ± 0.05 g (mean ± SE) contracture response to 1% halothane (8). These results provide strong evidence that rectus muscle may yield false positive contractures based on usual diagnostic criteria.

1% Halothane Plus Caffeine

It is difficult to draw conclusions and determine thresholds from the results of this test. The dose-response curve, instead of being typically steep, begins to increase at the lower caffeine concentrations and proceeds gradually upward. By 2 mM caffeine, a distinct increase does occur, which agrees with the mean HCSC value for vastus muscle but not with that for rectus muscle. However, because of the gradually changing initial slope, a reliable lower limit for normal muscle was not found. As with the caffeine-alone

test, the HCSC values for the vastus and rectus muscles were significantly different from each other.

Clinical Considerations

For diagnostic purposes, most laboratories routinely use vastus muscle. Based on this study, our laboratory will continue to do so because use of rectus abdominis muscle would yield a wider variation of results and, therefore, would complicate analysis, particularly when considering contracture responses to halothane alone.

The following discussion uses data from our MH diagnostic biopsy patients. With the caffeine alone test, among those patients who were diagnosed as MH positive, 40% of bundles had 7% rise thresholds <2 mM and 69% of bundles had CSC values <4 mM. MH negative patients had 7% rise thresholds ≥2 mM in all bundles and CSC values <4 mM in 6.6% of the bundles. The 7% rise threshold appeared to be less sensitive and more specific than the CSC.

In regard to halothane alone, earlier we used 2% halothane for 10 min, followed by 3% for 10 min. For the past year we have used only 3%. For patients diagnosed as MH positive, 73% of bundles exposed to 3% halothane showed a contracture response >0.50 g (range 0.56 to 5.60 g); whereas with 2% halothane, only 35% of bundles showed a contracture response >0.50 g (range 0.66 to 1.44 g). With 3% halothane, every patient with a positive biopsy had at least one bundle, the contracture of which exceeded 0.50 g, but this was not true for 2% halothane. When examining results of patients who had negative diagnostic muscle biopsies, 1 of 115 bundles showed a contracture >0.50 g in response to 3% halothane (0.51 g); there were no such contracture responses to 2% halothane. On the basis of these findings, 3% halothane seems a more appropriate concentration for diagnostic use. The European Standards recommend 2% halothane (1), but we believe that 3% halothane also deserves to be examined as a diagnostic modality. The University of California at Davis diagnostic criteria for susceptibility are a >7% increase in tension at 2 mM caffeine-alone or a contracture to halothane 3% >0.5 g.

The 1% halothane plus caffeine test yielded HCSC values with excessive variability, making this threshold minimally useful. However, we noted that control and MH negative vastus muscle almost never increased more than 1% over the lowest tension value (fraction of peak tension method) in response to 1% halothane plus 0.25 mM caffeine. In contrast, 67% of MH positive bundles showed an increase in tension

of ≥2% in response to 1% halothane plus 0.25 mM caffeine. From this data, we conclude tentatively that if there is a 2% increase in tension on the fraction of peak tension curve associated with 1% halothane plus 0.25 mM caffeine, then this is positive for MH. However, 33% of MH positive bundles did not show this response and, therefore, if there is a <2% increase in tension at 1% halothane plus 0.25 mM caffeine, the muscle cannot be diagnosed as normal. This specific response may be useful in confirming the results of caffeine alone and halothane alone challenges.

Summary

1) The caffeine alone test is reproducible and minimally variable, and the fraction of peak tension method provides the most consistent threshold (a 7% increase in twitch tension occurs at concentrations of 2 mM or more in normal muscle). 2) Rectus abdominis muscle yields false positive results (with use of usual diagnostic criteria), especially with 3% halothane alone and caffeine alone testing. 3) 3% halothane alone appears to be a better indicator of MH susceptibility than 2% halothane alone. 4) 1% halothane plus caffeine testing shows potential sensitivity in identifying MH susceptible muscle at the 0.25 mM caffeine concentration. However, this test has certain specific limitations.

References

1. Ording H. Diagnosis of susceptibility to malignant hyperthermia in man. Br J Anaesth 1988;60:287–302.
2. Gronert GA. Contracture responses and energy stores in quadriceps muscle from humans age 7–82 years. Hum Biol 1980;52:43–51.
3. Gronert GA. Muscle contractures and adenosine triphosphate depletion in porcine malignant hyperthermia. Anesth Analg 1979;58:367–71.
4. Britt BA, Frodis W, Scott E, Clements MJ, Endrenyi L. Comparison of the caffeine skinned fibre tension (CSFT) test with the caffeine-halothane contracture (CHC) test in the diagnosis of malignant hyperthermia. Can Anaesth Soc J 1982;29:550–62.
5. Britt BA, Endrenyi L, Scott E, Frodis W. Effect of temperature, time and fascicle size on the caffeine contracture test. Can Anaesth Soc J 1980;27:1–11.
6. Brownell AKW, Paasuke RT, Elash RT, et al. Malignant hyperthermia in Duchenne muscular dystrophy. Anesthesiology 1983;58:180–2.
7. Nelson TE, Flewellen EH, Gloyna DF. Spectrum of susceptibility to malignant hyperthermia—diagnostic dilemma. Anesth Analg 1983;62:545–52.

8. Rosenberg H, Reed S. In vitro contracture tests for susceptibility to malignant hyperthermia. Anesth Analg 1983;62:415–20.

9. Ording H, Skovgaard LT. In vitro diagnosis of susceptibility to malignant hyperthermia: comparison between dynamic and static halothane and caffeine tests. Acta Anaesthesiol Scand 1987;31:458–61.

10. Ording H, Hansen U, Skovgaard LT. Age, fiber type composition and in vitro contracture responses in human malignant hyperthermia. Acta Anaesthesiol Scand 1988;32:121–4.

11. Moulds RFW, Denborough MA. A study of the action of caffeine, halothane, potassium chloride and procaine on normal human skeletal muscle. Clin Exp Pharmacol Physiol 1974; 1:197–209

12. Nelson TE, Austin KL, Denborough MA. Screening for malignant hyperpyrexia. Br J Anaesth 1977;49:169–71.

13. Larach MG for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. Anesth Analg 1989;69:511–5.

Nitrous Oxide Augments Sympathetic Outflow: Direct Evidence from Human Peroneal Nerve Recordings

Thomas J. Ebert, MD, PhD and John P. Kampine, MD, PhD

Direct evidence for postganglionic sympathetic nerve activation to blood vessels supplying skeletal muscle was sought by recording from the peroneal nerve of 13 volunteers with a 5-μ tipped tungsten needle. Eight subjects breathed through an anesthesia face mask connected to a semiclosed anesthesia circuit for two consecutive 10-min periods while 25% and 40% nitrous oxide (N_2O) was administered sequentially. Five subjects served as controls and breathed equivalent concentrations of nitrogen. Blood pressure and central venous pressure were recorded from radial artery and jugular vein catheters. Forearm blood flow was measured by venous occlusion plethysmography. Peroneal nerve recordings were amplified 100,000-fold and integrated for analysis of burst frequency. N_2O did not significantly alter respiratory rate, end-tidal CO_2 (mass spectrometry), and diastolic or central venous pressures but did produce small but significant increases in heart rate and systolic pressure compared to time-control (P < 0.05). In contrast, N_2O was associated with progressive, large increases in muscle sympathetic nerve activity (peak % Δ = 69 ± 22 burst/min [X ± sEM]) and forearm vascular resistance (30 ± 4%) and a nonsignificant increase in plasma norepinephrine levels. Thus, brief exposure to 25% and 40% N_2O produces striking increases in sympathetic outflow to skeletal muscle in humans.

Key Words: ANESTHETICS, GASES—nitrous oxide. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—nitrous oxide.

Nitrous oxide (N_2O) has been in clinical use for over a century. Its initial popularity as an analgesic agent stemmed from the belief that it had minimal cardiovascular effects. However, more recent data indicate that N_2O can produce myocardial depression when combined with intravenous narcotic agents (1,2) and may activate the sympathetic nervous system when given with inhalation anesthetics (3,4).

Indirect evidence of myocardial depression and simultaneous sympathetic activation has been obtained from volunteers breathing 40%–60% N_2O concentrations; this evidence is based on measurements with ballistocardiography (5), systolic time intervals (6), and forearm plethysmography (5), and by demonstrating increases in plasma catecholamine levels (5) and observing pupil dilation and sweating (7). The sympathetic excitation produced by N_2O is thought

to be unpredictable and may occur in intermittent bursts (8). It is usually most evident during the first 15–30 min of N_2O administration (5,7).

In the present research, a small epoxy-coated tungsten needle was inserted into the peroneal nerve of human volunteers to obtain direct and continuous measurements of postganglionic sympathetic outflow to blood vessels supplying skeletal muscles. These recordings were made before and during two consecutive 10-min periods of administration of 25% and 40% N_2O to volunteers to seek direct evidence of sympatho-excitation and to quantify its time course and magnitude.

Methods

Informed consent was obtained from 13 healthy volunteers who signed forms approved by the Institution's Human Research Review Committee. Eight subjects were randomly chosen to breathe 25% and 40% N_2O, and five were randomly chosen to breathe equivalent concentrations of nitrogen (N_2). A 20-gauge catheter was inserted in the radial artery for direct measurement of blood pressure. A second

catheter was inserted into the external jugular vein and advanced into an intrathoracic site to monitor central venous pressure. A bellows was strapped to the abdomen to record respiratory excursions. Forearm blood flow was measured using standard venous occlusion plethysmography employing a mercury-in-Silastic, temperature-compensated strain gauge and saddle placed about the forearm (9). Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow.

Multi-Unit Sympathetic Recordings

Peroneal nerve location was identified below the bony prominence at the head of the fibula on the lateral aspect of the lower leg by application of brief (0.1 sec) electric pulses (40–60 V, 1 Hz) to a probe moved about the skin surface to elicit muscle contractions distal to the probe. The skin was cleansed, and two epoxy-coated tungsten microelectrodes with 5 μm exposed tips and 0.2 mm diameter shafts (Tektronics Medical Instruments, Iowa City, IA) were inserted in close proximity over the peroneal nerve. One microelectrode was advanced below the fibular head while impulses of 0.5 V (0.1 sec, 1 Hz) were applied through its tip. A nerve fascicle to muscle within the peroneal nerve was identified by visible twitches of a muscle group in the lower leg. Stimulation was then halted and the reference electrode advanced so its tip was near the recording electrode but not within the nerve. Electrical signals from both microelectrodes were fed through a custom-made differential preamplifier where signals common to both electrodes were cancelled (e.g., 60 cycle noise and electronic glitches). The remaining unique signal (from the microelectrode in the nerve) was amplified 1000-fold and fed to a custom-made, rack-mounted, band-pass filter amplifier (400–2000 Hz) with a gain of 100. The signal was passed to a leaky integrator (0.1 sec time constant) and displayed on an oscilloscope. Signal discrimination was used for the audio output. Characteristic muscle sympathetic integrated bursts were sought by fine manipulations of the microelectrode within the muscle fascicle. These characteristics have been previously described and validated (10,11). Briefly, stretching muscles innervated by the nerve or tapping tendons of innervated muscles elicits afferent bursts of neural activity from mechano-receptors, whereas light stroking of the skin in the innervated area does not. Spontaneous efferent bursts of neural activity are augmented by the hypotension which occurs in phase 2 and 3 of the Valsalva maneuver and by the hypoxia and hypercarbia which occur during

Table 1. Baseline Data while Breathing 60% O_2 and 40% N_2

Measured Variable	Group 1 (Time Control)	Group 2 (N_2O)
R-R Interval (msec)	1046 ± 56	1055 ± 62
Standard Deviation of R-R Int. (msec)	64 ± 11	92 ± 14
Systolic Pressure (mm Hg)	127.5 ± 5.3	142.6 ± 4.3*
Diastolic Pressure (mm Hg)	61.5 ± 3.9	66.2 ± 3.2
Central Venous Pressure (mm Hg)	5.5 ± 0.4	3.6 ± 0.9*
Forearm Blood Flow (mL·min^{-1}·100 mL^{-1})	5.1 ± 1.2	5.3 ± 0.9
Forearm Vascular Resistance (mm Hg/(mL^{-1}·min^{-1}·100 mL^{-1})	21.4 ± 5.7	19.4 ± 4.2
Plasma Norepinephrine (pg/mL)	165 ± 33	114 ± 18
Muscle Sympathetic Activity (bursts/min)	17.7 ± 5.9	13.7 ± 3.6
(bursts/100 cardiac cycles)	25.3 ± 4.1	19.8 ± 3.8

Data are mean ± SEM.
*$P < 0.05$ vs time control.

prolonged voluntary apnea. Efferent bursts frequently occur in pulse-synchronous groupings and are often phase-locked to late expiration and early inspiratory efforts. Once an acceptable site for recording was located, subjects remained still and relaxed so as to not alter the microelectrode tip location.

Procedures

All subjects breathed through an anesthesia face mask connected to a semi-closed circle system. A mixture of 40% N_2 and 60% oxygen (O_2) was administered at 6 L/min for a 10-min control period. End-tidal gas concentrations were continuously monitored by mass spectrometry. Electrocardiogram (ECG), arterial and central venous pressure, respiration, and integrated muscle sympathetic nerve activity were sampled in real-time by a computer. Three-min epochs of data were dumped rapidly to disk and analyzed off-line. After two consecutive 3-min epochs of data were collected during the last 6 min of control, five subjects were selected to be time-controls and continued to breath the O_2/N_2 mixture for an additional 20 min. The other eight subjects breathed two concentrations of N_2O. Minutes 1–10 consisted of breathing 25% N_2O while minutes 11–20 consisted of breathing 40% N_2O. Forearm blood flow measurements were made at quiet baseline, at minutes 10–19 while breathing 25% N_2O, and at minutes 19–20 while breathing 40% N_2O. Central venous blood samples were obtained immediately after forearm
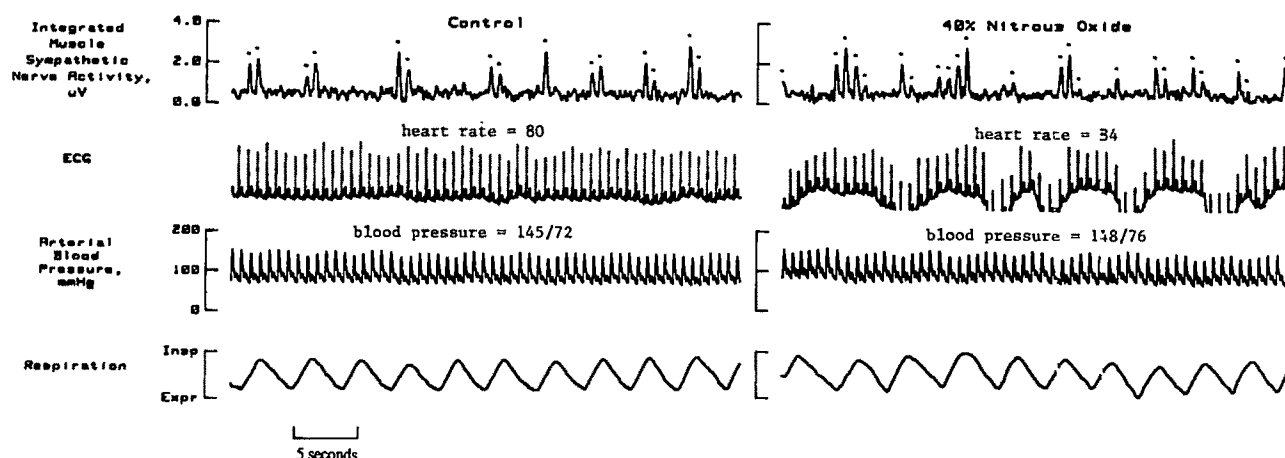
Figure 1. Representative recordings from one volunteer at baseline (control) while breathing 40% N_2 (left) and during administration of 40% N_2O (right). Characteristic integrated bursts of muscle sympathetic activity are identified by computer with a small dot placed above each burst. Respiratory rate and heart rate were essentially unchanged during N_2O administration. However, this subject became agitated and reported anxiety which resulted in a elevation of blood pressure and large fluctuations in ECG baseline which were not related to respiration. This probably reflects activation of skin sympathetic nerves.

blood flow measurements for determination of norepinephrine content.

Several indices of nerve activity were derived from computer analysis of 3 min sampling periods, including burst area, amplitude, bursts/100 heart beats, bursts/min, burst frequency/area, burst frequency/amplitude, etc. However, all calculated parameters showed quantitatively similar changes during experimental time periods. To avoid duplication of data and for simplicity of presentation only bursts/min and bursts/100 heart beats are presented.

Norepinephrine content of plasma was determined by high-pressure liquid chromatography. Data were compared with analysis of variance for repeated measures and Dunnett's t-tests. The null hypothesis was rejected if $P < 0.05$ were obtained. All data are presented as means ± SEM.

Results

The average age of volunteers was similar in both groups (mean = 21, range = 19–24), but the average weight in group 2 volunteers (N_2O) was significantly greater than in control subjects (82.3 ± 3.3 vs 70.9 ± 3.6 kg, respectively). Baseline data collected while subjects breathed a 40% N_2, 60% O_2 mixture by mask are shown in Table 1. The only significant differences

between groups at baseline were a lower systolic pressure and a higher central venous pressure in control subjects.

Two segments of recorded data from one subject are shown in Figure 1. An increase in the number of integrated sympathetic bursts is demonstrated in the right tracing during the administration of 40% N_2O. Heart rate and respiratory rate were changed minimally during N_2O. However, in this subject large fluctuations in ECG baseline occurred and blood pressure increased. This may have been due to activation of skin vasoconstrictor and/or sudomotor nerves coincident with the subject showing agitation and reporting excitement.

Figures 2–4 display the changes in all measured parameters which occurred during the 20-min testing period. R-R intervals on the ECG decreased and systolic pressure was lower (Figure 2) during N_2O breathing compared to time controls ($P < 0.05$). There were no significant differences between groups in respiratory rate or end-tidal Pcc_2 during these studies. Forearm blood flow however, decreased 17 ± 3% (X ± SEM), forearm vascular resistance increased 30 ± 4% and plasma norepinephrine content was elevated by 46 ± 17% during N_2O administration (Figure 3). Moreover, there were large progressive increases in muscle sympathetic activity (Figure 4) in subjects receiving N_2O (expressed as either burst/min or /100 heart beats).

Discussion

The present study demonstrates that brief exposure to N_2O in healthy humans results in activation of sympathetic efferent nerve activity directed to the vasculature supplying skeletal muscle. This is the first direct evidence in human beings or animals of
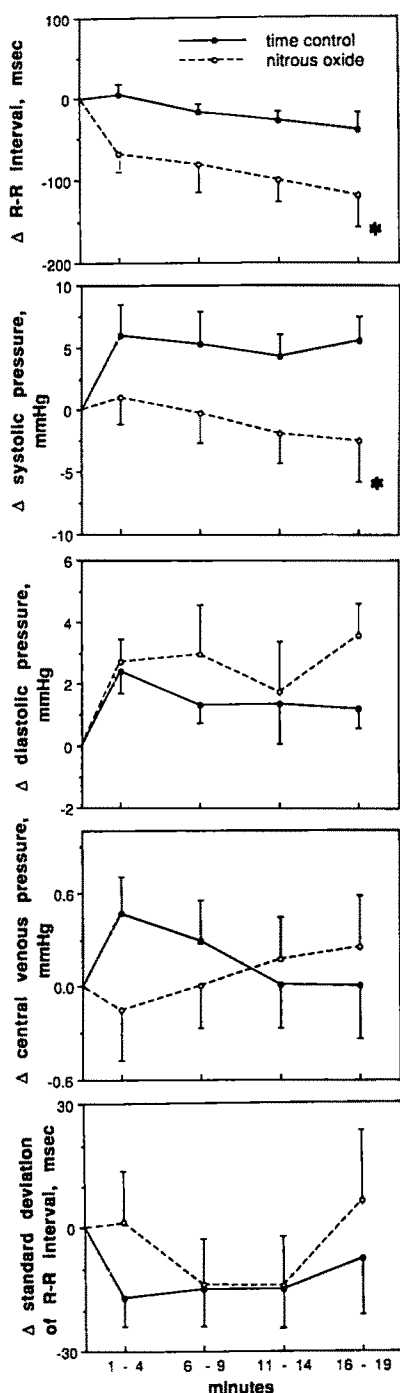
Figure 2. Changes (from control) in measured parameters while breathing 25% and 40% N$_2$ (time control) or 25% N$_2$O (min 1–10) and 40% N$_2$O (min 11–20). *Significant interaction (different responses between groups) at $P < 0.05$ level.

Figure 3. Forearm blood flow measurements and plasma norepinephrine levels were determined at min 9–10 while breathing 25% N$_2$ (time control) or 25% N$_2$O and at min 19–20 of the testing protocol while breathing 40% N$_2$ (time control) or 40% N$_2$O. The slope of the forearm blood flow and resistance responses were significantly different between groups (by ANOVA at $P < 0.01$ (**) level.

sympatho-excitation produced solely by N$_2$O. There were striking progressive augmentations in muscle sympathetic outflow associated with increasing concentrations of N$_2$O. This coincided with large increases in forearm vascular resistance and small elevations of plasma norepinephrine content.

Previous reports indicate that administration of 40% N$_2$O for 40 min to healthy volunteers increased urinary catecholamine levels, plasma norepinephrine concentrations, and peripheral vascular resistance (5). However, N$_2$O may inhibit the uptake of norepinephrine by the lung (12). Thus, the peripheral vasoconstrictor effects seen with N$_2$O might possibly be due simply to the delayed clearance of norepinephrine from the circulation. More direct evidence for sympathetic stimulation by N$_2$O has been derived from cats receiving a basal anesthetic of halothane in which administration of N$_2$O resulted in increases in preganglionic splanchnic sympathetic nerve activity and blood pressure (13). Evidence for sympatho-excitation in human beings anesthetized with halothane has been provided from studies in which the addition of 70% N$_2$O caused elevations of blood pressure, systemic vascular resistance, plasma norepinephrine, and esophageal temperature, as well as pupil dilation (3,4). A recent review of the literature by Eisele (14) indicates that the addition of 50%–70% N$_2$O to any of the potent volatile agents results in an increase of systemic vascular resistance and blood pressure.
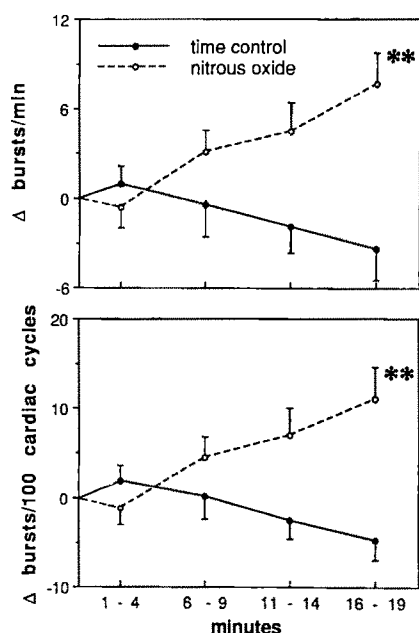
Figure 4. Progressive significant augmentations in muscle sympathetic nerve activity (bursts/min or bursts/100 cardiac cycles) occurred during administration of 25% N_2O (min 1–10) and 40% N_2O (min 11–20) compared to time control volunteers who breathed 25% and 40% N_2. The slopes of the responses between groups were significantly different (** $P < 0.01$).

Previous data suggest that the sympatho-excitation during N_2O anesthesia may be more pronounced during the early periods of exposure. For example, plasma norepinephrine levels are higher at 15 min than at 45 min during continuous administration of 40% N_2O to volunteers (5). Moreover, cardioacceleration and increases in blood pressure are reported to be most pronounced during the first 15–30 min of 2-hr exposures to 60% N_2O in humans (7). The experimental protocol of the present study consisted of relatively brief administration of N_2O to focus on this early interval of high probability for sympatho-excitation. Longer periods of exposure to N_2O would have been difficult to carry out. Subject cooperation and ability to remain completely immobile, which is essential for stable, quantifiable nerve recordings, become less reliable as the duration of the study is lengthened (particularly with volunteers in the semi-anesthetized state).

Eisele has noted that excitement is frequently seen with 30%–40% N_2O and has suggested that this can obscure cardiovascular changes (14). Moreover, there is evidence in pentobarbital-anesthetized dogs that administration of N_2O can result in unpredictable, episodic sympathetic discharge (8). This certainly was not evident in the muscle sympathetic nerves chosen for the present study. At these sites, progressive augmentations of sympathetic outflow were noted. However, sympathetic discharge to other regions

such as the skin, which is known to be influenced by arousal, may be more episodic. For example, all subjects in the present study were familiar with breathing through an anesthesia face mask and circuit and had participated in other invasive research in our laboratory, but none had previously been exposed to N_2O. Most of our subjects who received N_2O reported being relaxed and aware of an altered mental state, e.g., very distant surroundings, bizarre dreaming, or hyperacusis. Twc of the eight subjects reported excitement and showed agitation during the final few minutes of exposure to 40% N_2O. Although muscle sympathetic activation was not unusually pronounced in these individuals, heart rate and blood pressure increased and the electrocardiogram baseline showed large fluctuations which were unrelated to respiratory efforts (Figure 1). These responses can be attributed to activation of sympathetic nerves to skin with both vasoconstrictor and sudomotor activity, which can elicit an increase in blood pressure and can modify skin galvanic potentials (which influence the ECG baseline). The sympathetic augmentation during this excitement period may also have caused tachycardia. Since blood pressure was elevated in these two individuals, the failure of muscle sympathetic activity to decrease (via the baroreceptor reflex) suggests that central sympathetic drive to the muscle vasculature may also have been enhanced.

The standard deviation of consecutive R-R intervals is due to respiratory sinus arrhythmia and provides a quantitative window on fluctuations of vagal drive to the heart (15,16). Volunteers who received N_2O had a small increase in heart rate compared to the time-control group. However, there was no evidence for cardiac-vagal inhibition as changes in the calculated standard deviations during each 3-min sampling epoch were similar in both groups. This measurement is most valid when respiratory rate and tidal volume remain constant. The subjects who breathed N_2O showed only small increases in respiratory rate and decreases in alveolar Pco_2 that were not statistically different from control subjects.

In vivo studies in both human beings (5,6) and animals (8,17) suggest that N_2O is a myocardial depressant; however, simultaneous activation of the sympathetic nervous system offsets this depression. In the present study, central venous pressure did not increase as one might expect from the diminishment of cardiac pump performance. Moreover, despite rather striking increases in muscle sympathetic outflow and forearm vascular resistance during exposure to N_2O, there were only small increases in diastolic pressure and plasma norepinephrine levels. These were not statistically different from those observed in

control subjects. This suggests that N₂O may not produce a generalized sympathetic activation to all vascular beds (e.g., renal, mesenteric, etc.).

The mechanism for sympatho-excitation during N₂O administration is not known but may depend on suprapontine structures. In decerebrate cats exposed to N₂O, preganglionic splanchnic sympathetic activity decreases rather than increases (13). Another possible mechanism for the increase in sympathetic outflow produced by N₂O may be the inhibition of vagal afferent traffic from the heart, which elicits a reflex sympathetic discharge. This mechanism is suggested by data from dogs showing that exposure to 60% N₂O produced myocardial depression, reductions in cardiac output, and simultaneous elevations in mean arterial pressure. After surgical denervation of the heart, N₂O reduces myocardial function but does not increase blood pressure (17).

In conclusion, the present study indicates that brief administration of 40% N₂O to healthy volunteers increases efferent sympathetic nerve activity to skeletal muscle.

References

1. Stoelting RK, Gibbs PS. Hemodynamic effects of morphine and morphine-nitrous oxide in valvular heart disease and coronary heart disease. Anesthesiology 1973;38:45-52.

2. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular response. Anesth Analg 1979;58:390-5.

3. Bahlman SH, Eger EI II, Smith NT, et al. The cardiovascular effects of nitrous oxide-halothane anesthesia in man. Anesthesiology 1971;35:274-85.

4. Hornbein TF, Martin WE, Bonica JJ, Freund FG, Parmentier P. Nitrous oxide effects on the circulatory and ventilatory responses to halothane. Anesthesiology 1969;31:250-60.

5. Eisele JH, Smith NT. Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 1972;51:956-62.

6. Eriksen S, Johannsen G, Frost N. Effects of nitrous oxide on systolic time intervals. Acta Anaesthesiol Scand 1980;24:74-8.

7. Kawamura R, Stanley TH, English JB, et al. Cardiovascular responses to nitrous oxide exposure for two hours in man. Anesth Analg 1980;59:93-9.

8. Craythorne NWB, Darby TD. The cardiovascular effects of nitrous oxide in the dog. Br J Anaesth 1965;37:560-5.

9. Ebert TJ, Stowe DF, Barney JA, Kalbfleisch JH, Smith JJ. Summated responses of baroreflexes and thermal reflexes in man. J Appl Physiol 1982;52:184-9.

10. Ebert TJ. Reflex activation of sympathetic nervous system by ANF in humans. Am J Physiol 1988;255:H685-9.

11. Vallbo AB, Hagbarth KE, Turebjork HE, Wallin BG. Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. Physiol Rev 1979;59:919-57.

12. Naito H, Gillis CN. Effects of halothane and nitrous oxide on removal of norepinepherine from the pulmonary circulation. Anesthesiology 1973;39:575-80.

13. Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. Anesthesiology 1973;39:23-36.

14. Eisele JH. Cardiovascular effects of nitrous oxide. In: Eger, EI II, ed. Nitrous oxide/N₂O. New York: Elsevier, 1984:125-56.

15. Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. J Appl Physiol 1983;54:961-6.

16. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J Appl Physiol 1975;39:801-5.

17. Eisele JH, Trenchard D, Stubbs J, Guz A. The immediate cardiac depression by anesthetics in conscious dogs. Br J Anaesth 1969;41:86-93.

Antinociceptive Activity of Pentamorphone, a 14-β-Aminomorphinone Derivative, Compared to Fentanyl and Morphine

Frieda G. Rudo, PhD, Richard L. Wynn, PhD, Michael Ossipov, PhD, Robert D. Ford, PhD, Brenda A. Kutcher, Aaron Carter, and Theodore C. Spaulding, PhD

RUDO FG, WYNN RL, OSSIPOV M, FORD RD, KUTCHER BA, CARTER A, SPAULDING TC. Antinociceptive activity of pentamorphone, a 14-β-aminomorphinone derivative, compared to fentanyl and morphine. Anesth Analg 1989;69:450–6.

The analgesic potency of pentamorphone, a 14-β-aminomorphinone derivative, was compared to that of fentanyl and morphine by examining quantal dose–effect curves generated from data obtained in the mouse hot plate, rabbit tooth-pulp, and dog tail clamp tests. Onset and duration of antinociceptive effects were also compared. The ED_{50} values (mg/kg) were determined in mice for pentamorphone (0.0039), fentanyl (0.016), and morphine (7.3). In the rabbit tooth pulp test the ED_{50} values were 0.0009 mg/kg for pentamorphone, 0.0074 mg/kg for fentanyl, and 1.1 mg/kg for morphine; in the dog tail clamp test these values were 0.012 mg/kg for pentamorphone and 0.018 mg/kg for fentanyl. Duration of action (defined as the time until response to tooth pulp stimulation declined to 50% of maximum possible effect [MPE]) was 1C min with twice the IV ED_{50} for pentamorphone in mice. This duration was similar to that of the equipotent dose of fentanyl but much shorter than the duration of an equipotent potent dose of morphine (60 min). The duration in rabbits of the ED_{98} (IV) dose of pentamorphone was 65 min compared to 35 min for an equipotent dose of fentanyl and 200 min for morphine. Intramuscular doses of pentamorphone had significantly faster onset and shorter duration times than equipotent doses of morphine in both mice and rabbits. Pretreatment with naloxone in mice and rabbits attenuated the development of the antinociceptive effects of pentamorphone. This study shows that pentamorphone is a potent analgesic with a duration of action similar to that of fentanyl.

Key Words: ANALGESICS, PENTAMORPHONE.

Pentamorphone (14-β-pentylaminomorphinone) is a morphinan derivative with the IUOAC name 7, 8-didehydro-4,5-epoxy-3 hydroxy-17-methyl-14-(pentylamino)-(5)-morphinan-6-one (Figure 1), and its synthesis was first reported by Kobylecki et al. in 1979 (1). As pentamorphone is an opiate it was of interest to compare its antinociceptive action to that of fentanyl and morphine. The analgesic potency of pentamorphone was determined by examining quantal dose–effect curves generated from data obtained in the mouse hot-plate, rabbit tooth-pulp, and dog tail clamp tests. In addition, onset and duration of antinociceptive effects were determined in mice and rabbits. Pentamorphone produced strong antinociceptive effects at low doses in the three species, and these effects were prevented in mice and rabbits by pretreatment with naloxone. Pentamorphone compared favorably with fentanyl and morphine as an antinociceptive agent and, based on the models presented, has potential as a clinical analgesic.

Methods

Mouse Hot Plate

Antinociceptive activity was assessed in nonfasting male mice (Swiss–Webster) weighing between 18 and 22 g. The surface of a hot plate apparatus (Bel Arts Analgesia Meter T-475) was maintained at 55 ± 0.5°C. Concentrations of drugs to be tested were formulated
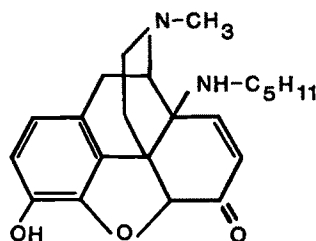
Figure 1. Chemical structure of pentamorphone (14-β-pentyl-amino morphinone).

as the salt and doses expressed as base. Naive mice were injected with saline (vehicle control) or drug solution (10 mL/kg) by either the intravenous (IV) or the intramuscular (IM) route of administration and then placed at various time intervals on the hot plate surface, and the time to the first paw lick response was recorded. Animals were removed from the hot plate immediately after a response or until the cut-off time of 30 sec was reached.

Potency determinations of the drugs were performed with IV injections. The drug was considered to produce analgesia in mice if the response latency was greater than two times the mean of the saline control group. To determine the median effective dose (ED_{50}), saline, pentamorphone, fentanyl, or morphine was injected into the lateral tail vein of groups of 10 mice. The following doses (mg/kg) were used: pentamorphone, 0.0001, 0.0025, 0.005; fentanyl, 0.01, 0.016, 0.025; morphine, 5.0, 8.0, 12.6. Each mouse was tested on the hot plate at 1 min after injection, and the numbers of mice exhibiting antinociceptive effects were plotted as percent affected versus dose. One minute represents the time at which onset occurs for opioid analgesics in the mouse after IV injection. Calculation of the quantal ED_{50} (95% C.L.) was by the method of Litchfield and Wilcoxin, fitted to a microcomputer (2), and was corrected for base content of salts.

Duration of action was determined in mice for IV and IM injections. IV doses were twice the ED_{50} ($2XED_{50}$) (mg/kg) for each drug (0.0078, pentamorphone; 0.016, fentanyl; 14.6, morphine) and 10 mL/kg for saline. IM doses were the IV ED_{98}, and $2X$ IV ED_{98} (mg/kg) of pentamorphone and morphine (0.15, 0.30 pentamorphone; 7.5, 15 morphine). Ten mice were injected per dose. Duration was defined as the time, in minutes, for % maximum possible effect (% MPE) to decrease to 50%. The percent MPE was calculated as follows:

$$\%MPE = 100 \times \frac{\text{test latency (sec)} - \text{vehicle latency (sec)}}{\text{cutoff latency (sec)} - \text{vehicle latency (sec)}}$$

Repeated latency measurements were taken in the same mice at predetermined time periods after injec-

tion. These times were 1, 2.5, 5, 10, 15, 20, 30, 45, and 60 min.

To determine the effect of naloxone on the analgetics, mice were divided into eight groups of 10 mice each. Of these, four groups received IV injections of either saline (10 mL/kg), or $2XED_{50}$ of morphine (14.6 mg/kg), fentanyl (0.032 mg/kg), or pentamorphone (0.0078 mg/kg) 1 min prior to testing on the hot-plate. An additional three groups were pretreated with naloxone (1 mg/kg, IP) 1 min before administration of analgetic agent, and one group received only naloxone 16 min before testing. Hot-plate latencies were determined 1, 2.5, 5, and 10 min after the last injection. For this study a 34 sec cutoff time was used.

Rabbit Tooth Pulp

ED_{50} values for each of the compounds were determined in New Zealand white rabbits of either sex, 1.5–2 kg, using a tooth pulp assay (3). A linear ramp function stimulator was used as the voltage source (4) with direct current being applied to previously exposed tooth pulps via fine wire platinum electrodes inserted and manually held into each cavity. The linearly increasing voltage was applied at a rate of 0.33V/sec until a lick/chew response occurred. Threshold voltages were established for controls using an average of three determinations. After drug or saline treatment a single determination was made, and the maximum stimulus was 10 V. Rabbits having control values greater than 5 V were excluded from the study. The animals served as their own control. Threshold voltages were determined before treatment (CV) and 5 min after IV administration of test drug (TV). Five minutes represents the time at which onset occurs for opioid analgesics in the rabbit after IV injection. Test drugs used were pentamorphone (dose–range = 0.0005–0.003 mg/kg), fentanyl (dose–range = 0.008–0.04 mg/kg), and morphine (dose–range = 1.2–3.0 mg/kg). Antinociceptive effect was defined as TV/CV of 2.0 or more, and the number of rabbits exhibiting analgesia was plotted as percent affected versus dose. The ED_{50} with 95% confidence limits and ED_{98} values were calculated using a standard computer program of the method of Litchfield and Wilcoxon fitted to a minicomputer (2). The ED_{50} values were expressed in terms of the base compound for each drug.

For duration studies in rabbits, groups of three to six female New Zealand white rabbits received the IV ED_{98} dose of pentamorphone, fentanyl, or morphine. Tooth pulp stimulation was applied at various time intervals after injection, and %MPE was calculated.

These times were 1, 2.5, 5, 10, 20, 30, 45, 60, 75, 90 min, then every 30 min up to 200 min. Duration was defined as the time until response declined to 50% MPE. Percent MPE was determined by the following formula:

$$\%MPE = \frac{TV - CV}{10V - CV} \times 100$$

Where TV = threshold voltage required to produce a lick-chew response, CV = pretreatment control voltage, and 10V = the cutoff voltage.

Durations of action of IM pentamorphone and morphine were determined in rabbits using the IV $2XED_{50}$ and ED_{98} doses (0.0018 mg/kg, 0.0058 mg/kg for pentamorphone; 2.2 mg/kg, 10.9 mg/kg for morphine).

To determine the effect of naloxone on the analgetics in rabbits, naloxone (0.01 mg/kg) was injected into three groups of eight rabbits. At 5 min, tooth pulp thresholds were measured and each group of rabbits received either pentamorphone (0.004 mg/kg), fentanyl (0.0296 mg/kg), or morphine (4.0 mg/kg). Thresholds were then measured after 10 min and compared to previous threshold values. A control experiment was carried out similar to the above except saline (10 mL/kg) replaced naloxone. Mean threshold voltages after treatments were compared to saline values using student's t-test.

Dog Tail Clamp

Mongrel dogs of either sex (10–20 kg), which responded by vocalizing or making an escape attempt to a Kelly clamp placed at the base of the tail for 30 sec, were selected for the study. Fentanyl or pentamorphone were administered into the saphenous vein and the antinociceptive effect was measured at 1, 5, and 10 min postinjection. The dog was considered to be analgetic if no response was made to tail clamp at either the 1-, 5-, or 10-min period. Data were calculated using a quantal analysis as described by Tallarida and Murray (2), and the ED_{50} was expressed as base content of drug.

Materials

Pentamorphone was obtained from Anaquest, Murray Hill, N.J., in crystalline form as the HCl salt. Morphine sulfate and fentanyl citrate were obtained from commercial sources. Naloxone was obtained as the commercial preparation (Narcan) from Dupont Laboratories.
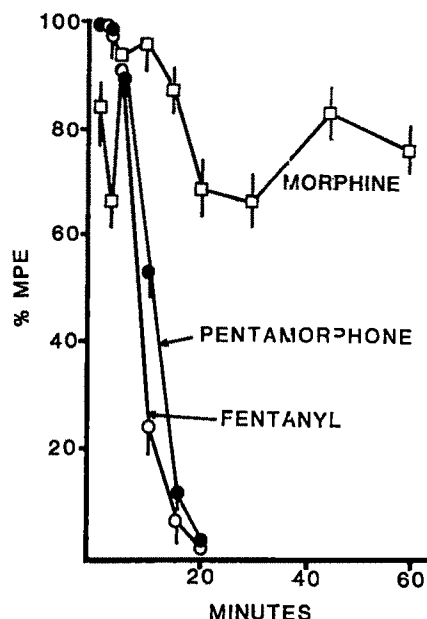
Figure 2. Duration of analgetic activity of IV administered pentamorphone (0.0078 mg/kg), fentanyl (0.032 mg/kg), and morphine (14.6 mg/kg) on the mouse hot-plate. Each drug was administered to groups of 10 mice. Bars represent standard error of the mean.

Institutional Approval for Animal Use

Protocols of animal use for this study were reviewed and approved by the Institutional Animal Care and Use Committee.

Results

Mouse Hot Plate

The ED_{50} values (mg/kg) and 95% C.L. from mouse hot plate were 0.0039 (0.003–0.006) for pentamorphone, 0.016 (0.014–0.021) for fentanyl, and 7.3 (5.3–10.3) for morphine. All three compounds had a rapid onset of antinociceptive activity in mice after IV administration of twice the ED_{50} dose (Figure 2). The saline-injected group had consistent paw-lick latencies which ranged between 15.9 and 18.7 sec over the 60-min time course. Maximal effects of pentamorphone, fentanyl, and morphine were found in the 1 to 5-min period after injection. The analgetic activity of pentamorphone and fentanyl disappeared rapidly as evidenced by the times of 10 and 8 min respectively to decline to 50% MPE. In contrast, at 60 min the % MPE of morphine was greater than 75%. Because of the contrast in duration of action between IV pentamorphone and morphine, comparisons were made in duration after IM administration. Maximal activity of pentamorphone (0.015 and 0.030 mg/kg) was reached within 5 min and for morphine (7.5 and
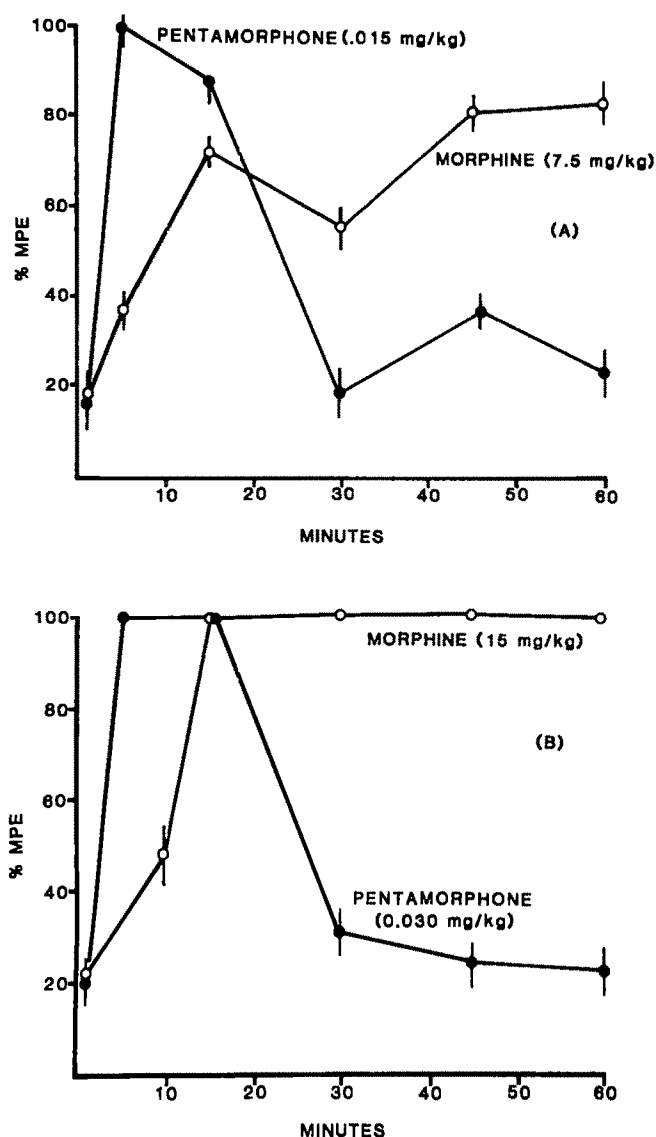
Figure 3. Duration of analgetic activity after IM administration of pentamorphone or morphine in the mouse hot-plate test. Ten mice were tested in each group. Bars represent standard error of the mean. (A) represents the IV ED_{98} dose and (B) 2× IV ED_{98} doses.

15 mg/kg) not until at least 15 min (Figure 3). The activity of pentamorphone disappeared relatively rapidly, and the time to 50% MPE was between 23 and 26 min for both doses. Morphine activity remained higher than 50% MPE up to 60 min after either dose. Pretreatment with naloxone 15 min prior to pentamorphone, morphine, or fentanyl attenuated the development of the antinociceptive effect of these agents (Figure 4). Naloxone alone (1 mg/kg IP) produced no effect on latency to paw-lick relative to the saline control. Groups which received combinations of naloxone and pentamorphone, fentanyl or morphine exhibited mean paw-lick latencies slightly lower than those of the saline group at 1 min and 10 min postinjection (≤0.05). The duration of naloxone's

antagonistic effect was sufficient to attenuate morphine-induced antinociception at the 10 min postinjection period (25 min postnaloxone).

Rabbit Tooth Pulp

ED_{50} values (mg/kg, IV) and 95% C.L. from rabbit tooth pulp were 0.0009 (0.0006–0.0075) for pentamorphone, 0.0074 (0.0065–0.0210) for fentanyl, and 1.1 (0.672–2.02) for morphine. The onset of antinociceptive activity occurred 1 min after IV administration of all three agents (Figure 5). The IV ED_{98} dose of pentamorphone elicited a duration of action to 50% MPE of 65 min compared to 35 min for fentanyl and 200 min for morphine.

When compared to morphine, pentamorphone had a more rapid onset and shorter duration after IM injection (Figure 6). The lower IM dose of pentamorphone (0.0018 mg/kg) elicited a peak effect four times more rapidly than the equivalent dose of morphine; the higher dose (0.0058 mg/kg) 10 times more rapidly. The durations of action of IM pentamorphone to 50% MPE were 65 min and 90 min for 0.0018 and 0.0058 mg/kg, respectively. The duration of IM morphine exceeded 120 min after doses of 2.2 and 10.9 mg/kg. Pretreatment of rabbits with naloxone 5 min before pentamorphone, morphine, or fentanyl attenuated the development of the antinociceptive effects of these agents at 10 min (Figure 7). Naloxone alone (0.01 mg/kg) produced no effect on tooth pulp thresholds relative to saline control. Rabbits that received combinations of naloxone and pentamorphone, fentanyl, or morphine exhibited no significant differences in mean thresholds voltages to saline. Mean threshold voltages in rabbits receiving compound alone, however, were significantly greater than saline ($P \leq 0.05$).

Dog Tail Clamp

Pentamorphone inhibited the tail clamp response in the dog with an ED_{50} of 0.012 mg/kg (0.008–0.017). IV fentanyl inhibited this response with an ED_{50} of 0.018 mg/kg (0.013–0.022).

Discussion

Pentamorphone (14-β-pentylaminomorphinone) is a morphine congener derived from thebaine. It is a member of the 6-ketomorphinones, which, as a group, are several times more potent than morphine

1 MIN. POST-INJECTION
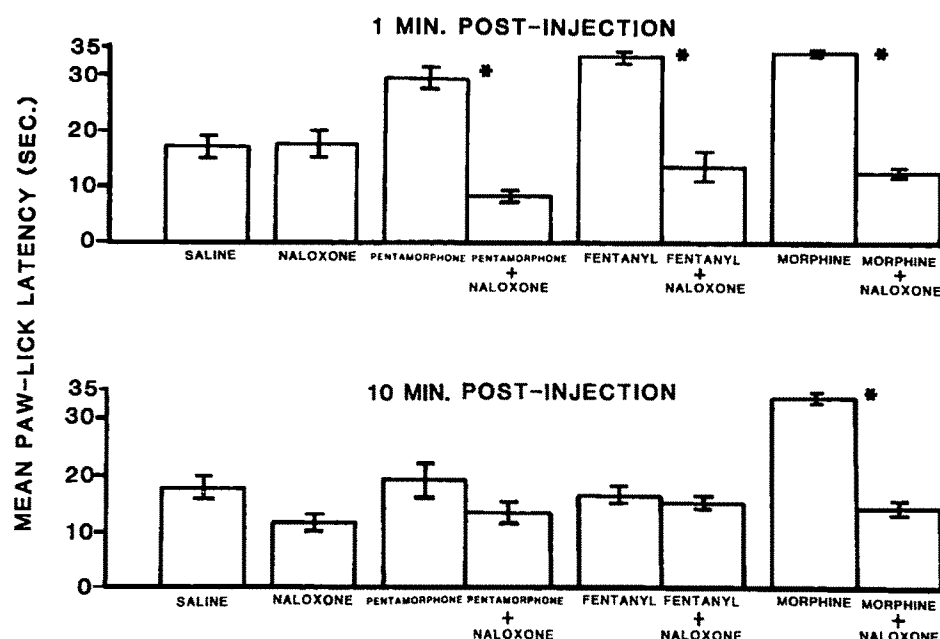
Figure 4. Representation of paw-lick latencies (sec) 1 and 10 min after IV injection of saline (10 mL/kg), pentamorphone (0.0078 mg/kg), fentanyl (0.032 mg/kg), and morphine (14.6 mg/kg). Naloxone (1 mg/kg) was administered IP 16 min before paw-lick latencies were measured. n = 10 for each group. Bars represent standard error of the mean. Asterisked values are significantly different from saline (P ≥ 0.05, t-test for matched pairs).

10 MIN. POST-INJECTION
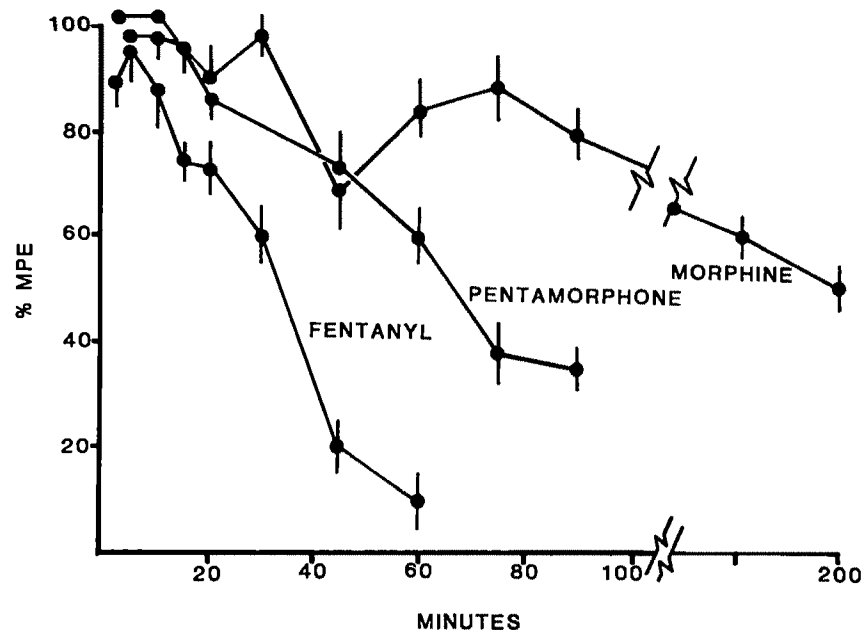
Figure 5. Duration of analgesia in the rabbit tooth pulp assay after IV dosing of pentamorphone, fentanyl, and morphine. Each value was the mean percent ± SE of four to six rabbits. The dose for each compound was the IV ED_{98} derived from dose–response curve data. Rabbits received either pentamorphone (0.0058 mg/kg), fentanyl (0.081 mg/kg), or morphine (10.9 mg/kg).

in antinociceptive activity as determined by the mouse hot plate assay (5). In particular, 14-amino congers are reported to have very high affinities for opiate receptors in rat brain homogenates (6). The present study showed pentamorphone to be an extremely potent antinociceptive agent in mice and rabbits. The ED_{50} of pentamorphone determined from the mouse hot-plate was 1872 times more potent than morphine and four times more potent than fentanyl. Rabbit data showed pentamorphone to be 1222 times more potent than morphine and eight times more potent than fentanyl. The ED_{50} values for

tail clamp inhibition in dogs were similar for pentamorphone and fentanyl. This was surprising in view of the data from mice and rabbits. The lack of potency differences may be indicative of the inability of a mechanical-pressure pain model to discriminate between these two analgesics. These compounds should be evaluated in additional pressure pain models in order to attempt explanation of the present findings. Morphine elicits extremely bizarre effects in mongrel dogs, including excitement, thrashing, and vocalization. Therefore, we considered it a poor candidate to be used as a standard in this model.
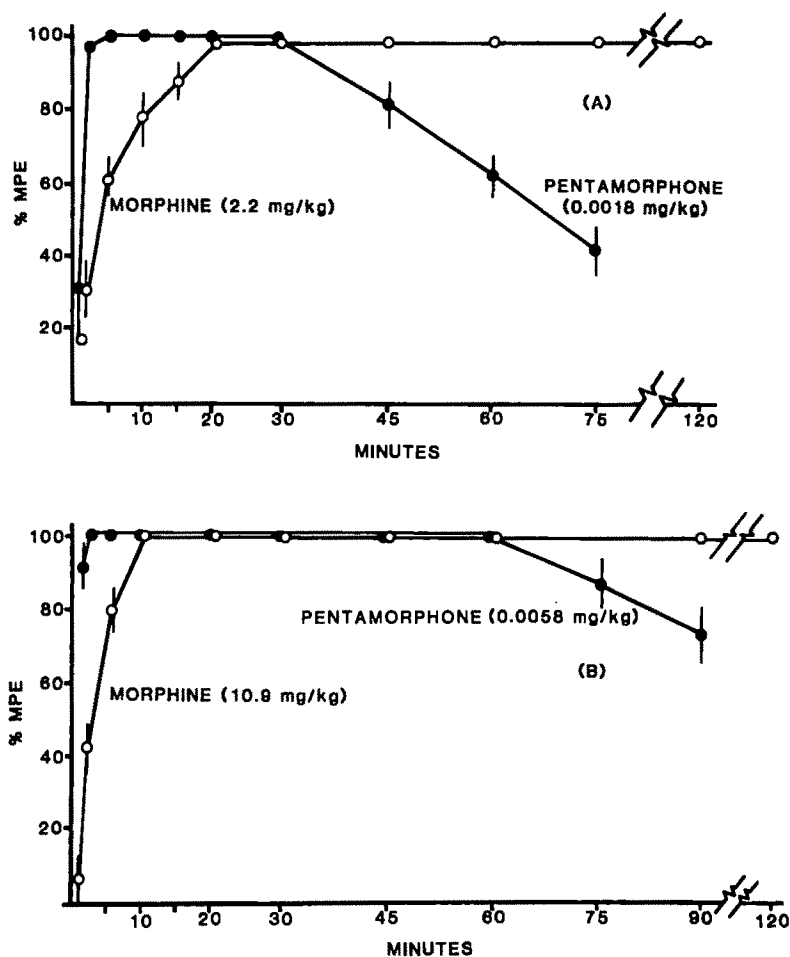
Figure 6. Duration of analgesia in the rabbit tooth pulp assay after IM dosing with pentamorphone and morphine. Each value was the mean percent of six rabbits. The dose of each compound was (A) 2× IV ED_{50} dose or (B) the IV ED_{98} dose derived from dose–response curve data.
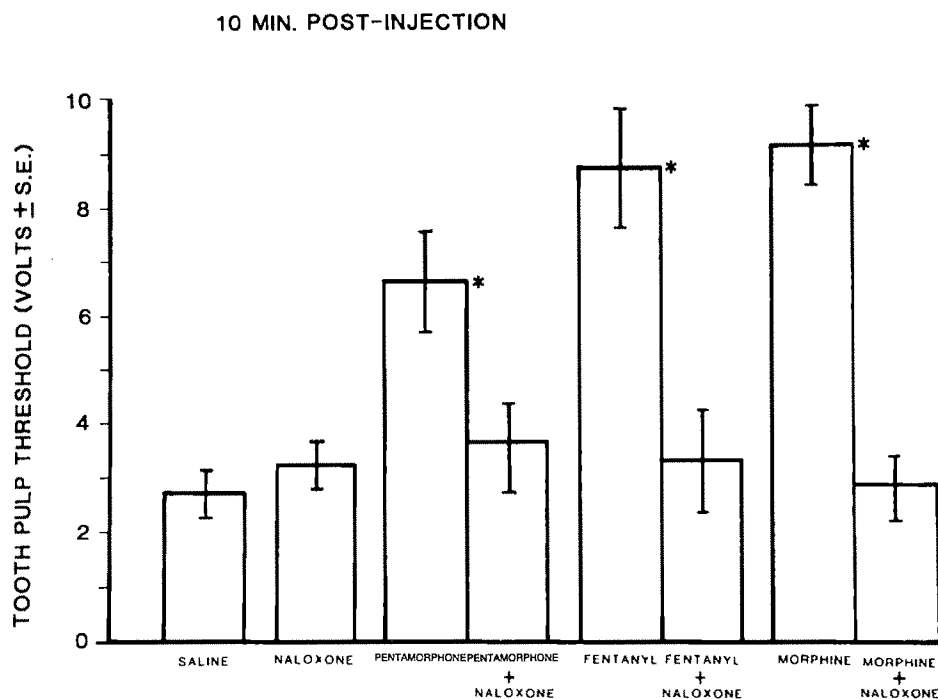
Figure 7. Representation of tooth pulp thresholds (volts) 5 min after IV injection of saline (10 mL/kg), pentamorphone (0.004 mg/kg), fentanyl (0.0296 mg/kg), and morphine (4.0 mg/kg). Naloxone (0.01 mg/kg) was administered IV 5 min before threshold voltages were measured. $n = 8$ for each group. Bars represent standard error of the mean. Asterisked values are significantly different from saline ($P \leq 0.05$, students t-test for matched pairs).

10 MIN. POST-INJECTION

Pentamorphone had a rapid onset of antinociceptive activity after IV injection in both mice and rabbits. Its duration of action after IV injection was similar to that of fentanyl in mice but twice that of fentanyl in rabbits. In each case, however, its duration was much shorter than that of morphine. Its rapid onset after IM administration was significantly faster than that of morphine in mice and rabbits. In fact, the high dose had as rapid an IM onset time (1 min) as that after IV injection in both species. The durations of action after IM doses were also significantly shorter than IM morphine.

Pentamorphone is a potent antinociceptive agent in mice and rabbits compared to morphine, having a significantly shorter duration of action after both IV and IM administration. An initial clinical evaluation (7) reports that pentamorphone appears to be analgesic with clinically tolerable side effects in the range of 0.12 to 0.24 μg/kg. Clinical analgesia was assessed by determining the maximum tolerance to periostial pressure over the anterior surface of the tibia and manbrium using a calibrated spring loaded rod. Also, this study suggested that the likely therapeutic range for postoperative pain was 0.05 to 0.2 μg/kg. Antinociceptive ED_{50} values in the three animal models reported in this paper are in fairly close agreement to the clinical doses, particularly the rabbit model (0.9

μg/kg). In view of its rapid onset of action after IM administration, and its antagonism by naloxone, it is worthy of further study as a potential candidate for clinical use as an analgesic agent.

References

1. Kobylecki RJ, Guest IG, Lewis JW, Kirby GW. Morphine derivatives. Chem Abs 1979;90:39100r.

2. Tallarida RJ, Murray RB. Manual of Pharmacologic Calculations with Computer Programs. New York: Springer-Verlag, 1981: 85-7.

3. Wynn RL, El'Baghady YM, Ford RD, Thut PD, Rudo FG. A rabbit tooth pulp assay to determine ED_{50} values and duration of action of analgesics. J Pharmacol Meth 1984;11:109-17.

4. Kidder GW III, Wynn RL. An automatic electronic apparatus for generating and recording a ramp stimulus for analgesia testing. J Pharmacol Meth 1983;10:137-42.

5. Schmidhammer H, Jacobson AE, Brossi A. Chemical and biological study of aromatic oxygenated 6-ketomorphinans. Med Res Rev 1983;3:1-19.

6. Rance MJ, Kobylecki RJ, Lane AC, Holdgate MJ, Barnard EA. Advances in Endogenous Opioids. Proceedings of the Twelfth International Narcotics Research Conference, 1981, 408-10. Edited by Takagi, Hiroshi: Simon, Eric J. Kodansha: Tokyo, Japan.

7. Glass PSA, Camporesi EM, Shafron D, Quill T, Reves JG. Evaluation of pentamorphone in humans: a new potent opiate. Anesth Analg 1989;68:302-7.

Spinal Needle Determinants of Rate of Transdural Fluid Leak

L. Brian Ready, MD, FRCP(C), Steven Cuplin, MD, Richard H. Haschke, PhD, and Michael Nessly, BS

READY LB, CUPLIN S, HASCHKE RH, NESSLY M. Spinal needle determinants of rate of transdural fluid leak. Anesth Analg 1989;69:457–60.

Using a new in vitro model and samples of human dura, a number of factors related to spinal needle design and use were examined with respect to their effects on the rate of transdural fluid leak. These included needle size, bevel design, bevel orientation, and angle of approach. Using 25-gauge Quincke needles, a 30° approach caused a rate of leak across the dura significantly less than those following 60° and 90° approaches. A significant increase in leak rate was found with 22-gauge Quincke needles when the bevels were oriented so as to be perpendicular rather than parallel to the long axis of the dura. Also, 22-gauge Whitacre needles caused significantly less leak than did 22-gauge Quincke needles, and 25-gauge Quincke needles produced significantly less leak than 22-gauge Quincke needles. If human dura behaves in vivo as it does in this in vitro model, it would be advantageous to perform lumbar puncture using oblique approaches and small needles with conical tips.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—needles.

The correlation between spinal needle size and the incidence of post-lumbar puncture (PLP) headache is well known (1), and is presumed to reflect the rate of leak of cerebrospinal fluid (CSF) through a hole in the dura. Less information is available concerning other factors that may influence CSF leak and the incidence of PLP headache. These factors may include the angle of approach of the spinal needle to the dura, orientation of the needle bevel relative to the long axis of the dura, and design of the tip of the needle.

The angle of needle approach was correlated with the rate of CSF leak and the incidence of PLP headaches by Hatfalvi, who reported no headaches in a series of more than 600 subarachnoid blocks with 20-gauge needles using a lateral approach (2). Subsequent in vitro studies led Hatfalvi to conclude that the absence of headaches in his patients was due to reduced CSF leak associated with the use of the lateral approach and the associated angle at which the needle punctured the dura (2).

References that span six decades describe a longitudinal orientation of human dural fibers (3,4), and state that inserting a spinal needle bevel parallel to

these fibers is recommended as a means to reduce CSF leak. However, only one report has documented longitudinal dural fibers (5), and one other has evaluated the effect of needle bevel orientation on transdural leak rate (6). Mihic (4), using 22- and 25-gauge spinal needles, and Norris et al. (7), studying inadvertent dural puncture with 17- and 18-gauge epidural needles, found a reduced incidence of headache associated with bevel orientation parallel to the long axis of the dura.

Needles that have conical points but no cutting bevel stretch and spread tissues apart rather than cut them. Greene in 1926 advocated the use of a conical needle point based on in vitro observations (3). Hart and Whitacre reported a 50% reduction in the incidence of headaches after introducing such a needle in their practice (8). Haroldson reported a decrease in headaches from 32% with bevelled needles to 9% using noncutting needles in obstetric patients (9).

The purpose of this study was to examine in an in vitro model of human dura the relationship between the rate of transdural leak and four variables—needle size, angle of the needle penetrating the dura, bevel orientation relative to the long axis of the dura, and needle point design.

Methods

Samples of dorsal lumbar dura (L2–L5) with attached arachnoid membranes were obtained at autopsy from

10 human cadavers. The specimens were easily identified and atraumatically harvested following removal of the vertebral bodies by an autopsy technician. The specimens were immediately placed in preservative-free normal saline and were studied within 1 hr.

Each specimen was mounted over the open end of a chamber with an attached vertical column. A machined collar applied uniform tension to the edges of a portion of each specimen to seal it to the chamber. The chamber and column were filled with normal saline to a height of 150 mm above the specimen to produce fluid pressure against the specimen equal to lumbar CSF pressure in the lateral recumbent position (10). A solitary puncture with the needle to be studied was made in the specimen. By mounting each needle on a stereotactic frame, bevel orientation, angle of approach, and advancement through the dura were precisely controlled. After each puncture, the needle was removed and the specimen was moved to place a fresh portion of dura under the collar. The 10 specimens of dura thus yielded a total of 81 puncture sites.

Three spinal needle types were studied: a Becton-Dickenson (B-D) 25-gauge standard (Quincke) design, a B-D 22-gauge Quincke, and a Monoject 22-gauge pencil point (Whitacre) design. Individual needles were used for several punctures and discarded before becoming dull. Using a stopwatch, the time required for the first milliliter of fluid to leak across the puncture site was recorded, and a leak rate was calculated (60 sec ÷ number of seconds for first mL of fluid to leak = leak rate in mL/min).

The 25-gauge B-D Quincke needles were used to study the effects of needle angle on leak rate. The bevels were all oriented parallel to the long axis of the dura. Angles of approach of 90°, 60°, and 30° were evaluated. The 22-gauge B-D Quincke needles were used to examine the influence of bevel orientation on transdural leak. The angle of approach to the dura with each needle was constant at 90°. A 22-gauge Whitacre needle was chosen to evaluate the effect of a conical needle point design on fluid leak. A constant 90° angle of approach was used. To examine the effect of needle size, we compared the leak rate after 22-gauge Quincke puncture at 90° with bevel parallel to the long axis of the dura with the rate after 25-gauge Quincke puncture using the same angle and bevel orientation.

Since the group variances were markedly unequal, the square root transformation was employed to correct for this heteroscedasticity. Analysis of variance with the Student–Newman–Keuls multiple range test was applied to the transformed data. An experiment-wide critical significance level of 0.05 was used. Seven contrasts of interest were determined a priori (11).

Results

Angles of Approach

The mean leak rates (mL/min), as defined above, ±SD with the 25-gauge Quincke needles with bevels oriented parallel to the long axis of the dura were 3.3 ± 1.6, 2.5 ± 1.2, and 0.3 ± 0.4 following 90°, 60°, and 30° punctures. The difference between the 90° and 60° leak rates was not significant. The 30° rate was significantly less than the 90° or 60° rates. Some leak was present following all punctures made at 90° or 60°. In four of 10 of the 30° punctures, there was no measurable leak during the first minute of observation.

Bevel Orientation

Mean leak rates with 22-gauge Quincke needles penetrating the dura at 90° were 15.5 ± 3.3 and 11.9 ± 3.5 for the perpendicular (relative to the long axis of the dura) and parallel bevel orientations, respectively. This difference was statistically significant.

Needle Point Design

The mean leak rate with the 22-gauge Whitacre needle punctures at 90° was 7.7 ± 2.0. This was significantly less than the rates for the 22-gauge Quincke punctures at 90° with either parallel or perpendicular bevel orientation.

Needle Size

The mean leak rates after 22- and 25-gauge Quincke needle punctures at 90° with parallel bevel orientation were 11.9 ± 3.5 and 3.3 ± 1.6, respectively, a statistically significant difference. The data and levels of significance for the above comparisons are presented graphically in Figure 1.

Discussion

In this in vitro model of dural puncture, a 30° angle of approach to the dura with 25-gauge Quincke needles resulted in significantly lower leak rates than with the

Figure 1. Transdural fluid leak (mL/min) after spinal needle puncture. Values are mean ± SD.
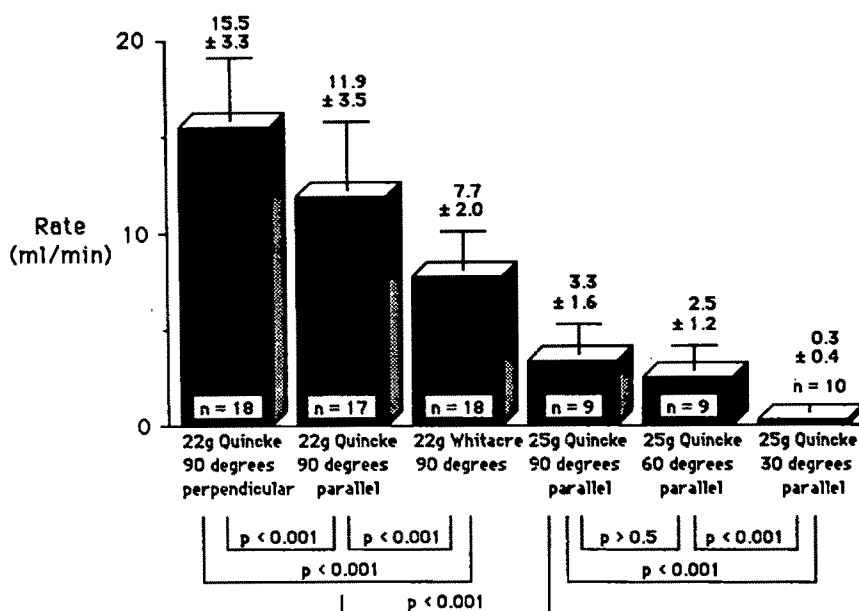
same needles used to puncture the dura at 60° or 90°. This finding is in agreement with the work of Hatfalvi (2). A possible explanation for this difference is that an oblique needle track through a thick membrane such as the dura may tend to seal itself via a flap valve mechanism. Such a flap would tend to close when fluid pressure is applied to one side of the membrane. In addition, the holes made in the dura and arachnoid membranes may be offset enough following an oblique needle puncture to provide a second flap valve mechanism.

Changes in bevel orientation had a statistically significant effect on leak rates when the punctures were made at right angles to the dura with 22-gauge Quincke needles. Traditional teaching of the existence of a longitudinal arrangement of dural fibers has not been conclusively demonstrated. Fink and Walker reported no preferential parallel arrangement of fibers in dura examined using light microscopy (12). Cruickshank and Hopkins (6), using 22-gauge Quincke needles and an in vitro dura model found no advantage to parallel bevel orientation as a means of reducing fluid leak, but Mihic (4) and Norris et al. (7) demonstrated clinical benefits to the practice.

The 22-gauge conical point (Whitacre) needle was associated with significantly slower leaks than bevelled (Quincke) needles of the same caliber. This finding is in agreement with the laboratory work of Greene (3), and the clinical experience of Hart and Whitacre (8) who reported reducing the PLP headache rate by 50% in their institution after switching to conical point needles. Similarly, Horaldson reported a decrease in headaches from 32% with bevelled needles to 9% using noncutting needles in obstetric

patients (9). Pencil point needles are believed to make a small puncture, then stretch tissues apart to allow passage of the shaft. Provided the tissues are elastic and are not torn during stretching, they should recoil when the needle is withdrawn, leaving a smaller defect than a needle of similar size with a cutting bevel.

The model used in this study may not adequately mimic the in vivo situation. A segment of dura similar in size to those that we punctured would have a slight curvature in vivo, would have external supporting structures (epidural vessels, fat, laminae, and ligaments), and might not have uniform wall tension (12).

Our finding that leak rates using 25-gauge needles were lower than leak rates following puncture with 22-gauge needles is consistent with the clinical observation that small needles cause fewer PLP headaches. Our model for dural puncture therefore appears useful by allowing controlled, reproducible, and quantitative observations to be made regarding the influence of a variety of factors on transdural leak. If in vivo human meninges behave as they do in this in vitro model, it would be advantageous to perform lumbar puncture with an approach permitting oblique angles using small needles with conical tips. A 30° needle angle can be achieved clinically using a lateral approach for lumbar puncture (13).

References

1. Greene BA. A 26-gauge lumbar puncture needle: its value in the prophylaxis of headache following spinal analgesia for vaginal delivery. Anesthesiology 1950;11:464–9.

2. Hatfalvi BI. The dynamics of post-spinal headache. Headache 1977;17:64–6.

3. Greene HM. Lumbar puncture and the prevention of post-puncture headache. JAMA 1926;86:391–2.

4. Mihic DN. Postspinal headache and relationship of needle bevel to longitudinal dural fibers. Reg Anesth 1985;10:76–81.

5. Franksson C, Gordh T. Headache after spinal anesthesia and a technique for lessening its frequency. Acta Chir Scand 1946;94:443–54.

6. Cruickshank RH, Hopkinson JM. Fluid flow through dural puncture sites. Anaesthesia 1989;44:415–8.

7. Norris MC, Leighton BL, DeSimone CA. Needle bevel direction and headache after inadvertent dural puncture. Anesthesiology 1989;70:729–31.

8. Hart JR, Whitacre RJ. Pencil point needle in prevention of postspinal headache. JAMA 1951;147:657–8.

9. Haroldson S. Headache after spinal anesthesia: experiments with a new spinal needle. Anesthesiology 1951;12:321–7.

10. Davson H. Physiology of Cerebrospinal Fluid. London: J and A Churchill, 1977:377.

11. Zar JH. Biostatistical Analysis. Englewood Cliff, N.J.: Prentice Hall, 1974:151–5, 187–8.

12. Fink RB, Walker S. Orientation of spinal needle bevel: effect on fluid leak in a model. Reg Anesth 1987;12:45–6.

13. Kershner D, Shapiro AL. Interlaminar spinal anesthesia. An alternative lateral approach for subarachnoid puncture. Am J Surg 1946;72:43–6.

First-Pass Uptake of Verapamil, Diazepam, and Thiopental in the Human Lung

David L. Roerig, PhD, Karel J. Kotrly, MD, Christopher A. Dawson, PhD, Susan B. Ahlf, BA, John F. Gualtieri, BS, and John P. Kampine, MD, PhD

ROERIG DL, KOTRLY KJ, DAWSON CA, AHLF SB, GUALTIERI JF, KAMPINE JP. First-pass uptake of verapamil, diazepam, and thiopental in the human lung. Anesth Analg 1989;69:461-6.

The first-pass uptake of verapamil, diazepam, and thiopental in the human lung was determined using multiple-indicator dilution techniques. These three drugs represent lipid-soluble agents that differ in their ionic characteristics at physiological pH. Verapamil, a basic lipophilic amine, underwent significant uptake, with 50% of the drug accumulating in lung tissue during the first pass. With diazepam, a nonbasic lipophilic amine, there was 30% uptake during the first pass through the human lung—significantly less than that observed with verapamil. With thiopental, an acidic lipophilic barbiturate, only 14% of the injected drug accumulated in the lung during the first pass. Taken together, these data are consistent with observations from animal studies, which indicate that extensive pulmonary uptake is greater with basic amine drugs that are moderately to highly lipid-soluble. Also, the relatively high first-pass uptake of verapamil in the human lung suggests a quantitatively significant role of this nonrespiratory function of the lung in the early pharmacokinetics of intravenous verapamil.

Key Words: ANESTHETICS, INTRAVENOUS—diazepam, thiopental. LUNG, DRUG UPTAKE. PHARMACOKINETICS, VERAPAMIL, DIAZEPAM, THIOPENTAL.

A wide variety of endogenous and exogenous compounds accumulate in the lung tissue (1–5). For certain drugs this pulmonary accumulation is extensive with lung tissue to blood concentration ratios as high as 400 (4). Organic compounds containing a basic amine moiety and of moderate to high lipid solubility achieve the highest concentration in lung tissue (4,6–14). Uptake of these basic lipophilic amines is extensive and rapid, with high uptake observed in a single pass through the lung. Using multiple-indicator dilution techniques, it is possible to determine the extent of first-pass drug uptake in the human lung in patients undergoing anesthesia prior to surgery. Drugs such as lidocaine (15,16), propranolol (17), fentanyl (18–20), and meperidine (18) all exhibit a high first-pass uptake in the human lung. As a result, only 20% to 40% of the dose of these drugs enters the systemic circulation immediately after intravenous administration. With this high first-pass uptake, the lung essentially acts as a capacitor limiting the rate at which the injected dose enters the systemic circulation. This could play a role in the early pharmacokinetics of certain drugs and possibly the time to onset of pharmacological action. Recently we reported first-pass pulmonary uptakes in human subjects for fentanyl, meperidine, and morphine of 75%, 65%, and 4%, respectively (18). These narcotics are basic amines (pKa values of 7.9–8.5), but fentanyl and meperidine are 676 and 28 times more lipid-soluble than morphine. This indicates that high lipid solubility of the drug is essential for extensive accumulation in the human lung.

In the present study we investigated the influence of the ionic properties of lipid-soluble drugs on pulmonary drug uptake. For this purpose, we determined the first-pass uptake in the human lung of a basic lipophilic amine, verapamil, a nonbasic lipophilic amine, diazepam and a lipophilic acidic drug, thiopental.

Table 1. Summary Data for First-Pass Pulmonary Drug Uptake

Drug	n	Age (yr)	Body Weight (kg)	CO (L/min)	Lung Uptake (% Injected)
Verapamil	6	64 ± 2	75 ± 5	5.31 ± 0.31	48.1 ± 3.4
		(57–68)	(59–91)	(4.73–6.80)	(34.6–58.8)
Diazepam	9	57 ± 3	81 ± 7	6.42 ± 0.72	30.4 ± 3.7*
		(39–67)	(50–110)	(3.35–10.3)	(8.33–42.5)
Thiopental	8	49 ± 5*	84 ± 4	6.84 ± 0.58	13.8 ± 1.8*†
		(33–67)	(67–100)	(4.87–9.87)	(4.97–19.7)

*Significantly lower than verapamil $P < 0.01$.
†Significantly lower than diazepam $P < 0.01$.

Methods

ASA physical status I–III subjects were studied before elective surgery. All studies were approved by and performed in accordance with the institutional policies on human experimentation, and informed consent was obtained from each patient. In none of the patients was there evidence of severe or moderate obstructive or restrictive lung disease revealed by clinical examination, chest x-ray, or by pulmonary function test on the day before surgery. Patients were selected to receive a specific drug based on their medical need and were divided into three groups according to the drug studied.

An arterial (radial) catheter, an electrocardiogram (chest lead 5), and central venous or pulmonary artery catheters were utilized for monitoring purposes, drug injections, and blood sample withdrawals. Preoperative medication was limited to 8 mg of morphine sulfate IM. Characteristics of the patients are shown in Table 1.

Measurement of First Pass Pulmonary Uptake

First pass drug uptake in the human lung was determined using a double indicator dilution method as previously described (18,20). Briefly, indocyanine green dye (ICG) (Cardiogreen, H.W.D., Baltimore) was used as the nonextractible vascular indicator. A 3 mL bolus solution was prepared containing ICG (15 mg), human serum albumin (300 mg), and verapamil (3.75 mg), diazepam (11.2 mg), or thiopental (37.5 mg). Two mL of this solution was injected through the central venous catheter and blood withdrawn from the radial artery (60 cc/min) and collected in 1 sec fractions for 45 sec as previously described (18,20). The total injected doses were 2.5 mg, 7.5 mg, and 25 mg of verapamil, diazepam, and thiopental, respectively. Methods of drug analysis and calculation of first-pass uptake are presented in the Appendix.
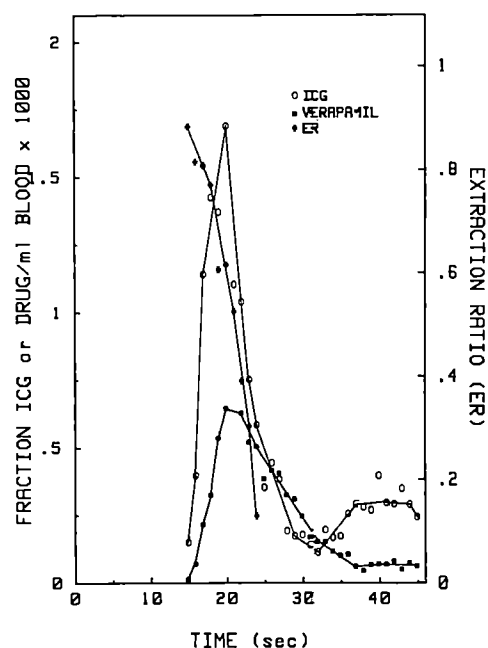
Figure 1. Fraction of injected dose of ICG (open circles) and verapamil (closed squares) per mL of arterial blood versus time (sec) after intravenous injection of the dye-drug bolus. Points denoted by # represent the extraction ratios (ER) for verapamil with time. Differences in area under the ICG and verapamil curves at 95% ICG recovery indicate 49.1% uptake of the injected verapamil during the first pass through the lung.

Results

The mean ± SEM body weight, age, and cardiac output (CO) in the three groups of patients are shown in Table 1 along with the range of these values in parentheses. No significant differences were observed in the variables between the three groups with the exception that the mean age of patients in the thiopental group was lower than the verapamil group. There was no correlation between CO and the extent of first pass uptake of these drugs.

Figures 1, 2, and 3 show typical first-pass uptake curves for verapamil, diazepam, and thiopental, respectively. Each figure represents the fraction of the
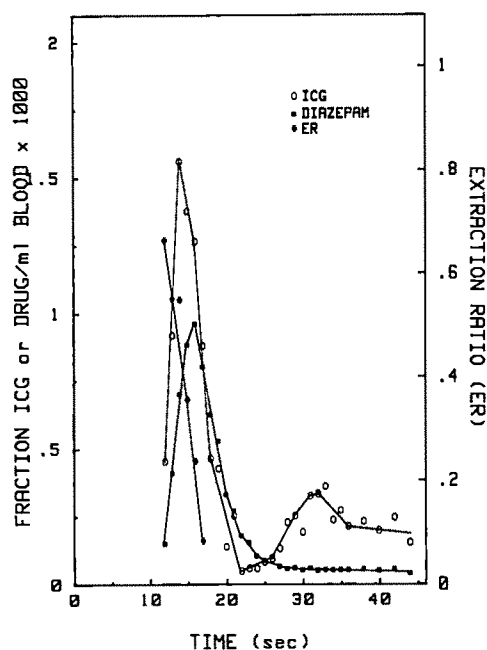
Figure 2. Fraction of injected dose of ICG (open circles) and diazepam (closed squares) per mL of arterial blood versus time (sec) after intravenous injection of the dye-drug bolus. Points denoted by # represent the extraction ratios (ER) for diazepam. Difference in area under the ICG and diazepam curves at 95% ICG recovery indicate 26.5% uptake of the injected diazepam during the first pass through the lung.

Figure 3. Fraction of injected dose of ICG (open circles) and thiopental (closed squares) per mL of arterial blood versus time (sec) after intravenous injection of the dye-drug bolus. Points denoted by # represent the extraction ratios (ER) for thiopental. Difference in area under the ICG and thiopental curves at 95% ICG recovery indicate 16.2% uptake of the injected thiopental during the first pass through the lung.

injected dose of ICG and drug per mL of blood vs time after injection of the dye-drug bolus. The data in these figures are from single patients in each group and represent the type of curve observed for that drug. In all three groups, the ICG curve peaked 14–19 sec after injection with a second smaller peak at 30–40 sec, which represented the recirculation of the ICG through the lung. Comparison of the fraction of injected ICG and verapamil recovered in arterial blood samples (Figure 1) demonstrated significant first-pass uptake of verapamil. For the patient shown, the first-pass uptake was 49.1%. For all patients in this group the mean ± SEM uptake of verapamil was 48.1 ± 3.4% of the injected dose (Table 1). The initial extraction ratio (ER) for verapamil was high (greater than 88%), but decreased rapidly with time, suggesting rapid equilibration between blood and lung tissue similar to that observed with other basic lipophilic amines such as lidocaine, fentanyl, and meperidine (15, 16, 18, 20).

An example of the first-pass pulmonary uptake of the nonbasic lipophilic amine, diazepam, in the lung is shown in Figure 2. In this patient the difference in area under the ICG and diazepam curves indicated that 26.5% of the injected diazepam accumulated in the lung during the first pass. For all patients in this group the mean first-pass uptake was 30.4 ± 3.7% of

the injected dose, which was significantly lower than for verapamil ($P < 0.01$). The initial extraction ratio was about 66% and declined as in the case of verapamil.

For the lipophilic but acidic drug thiopental (Figure 3) the first-pass uptake through the lung was 16.2% of the injected dose for the patient shown. The mean first-pass uptake of thiopental in the human lung for all patients in this group was 13.8 ± 1.8% of the injected dose which was significantly lower ($P < 0.01$) than the uptake of either verapamil or diazepam. The extraction ratio curves tended to follow the same pattern as that observed with verapamil or diazepam. As mentioned earlier, the mean age (49 ± 4.8 years) of patients in this group was statistically lower than that of the verapamil group because there were three younger patients in the thiopental group with ages of 33, 36, and 37. The percentage of thiopental taken up during the first pass for these patients was 12%, 5%, and 23%, respectively, with a mean of 13.3%. This is essentially the same as the mean uptake of thiopental for all patients in the group. Also, regression analysis of patient age vs percent uptake failed to reveal any relationship between thiopental uptake and age. Therefore, the lower uptake of thiopental in comparison to verapamil does not appear to be related to the difference in the mean age of the two patient groups.

Discussion

In the present study, we examined the first-pass uptake in the human lung of three lipophilic drugs that differ in their ionic character. For the basic lipophilic amine verapamil (pKa 8.5, octanol/water partition coefficient 67), 50% of the injected dose was taken up into the human lung during the first pass. This represents significant pulmonary accumulation with only half of the injected dose entering the systemic circulation immediately after injection. Based only on verapamil's lipophilic property, its uptake would be expected to be lower than that of fentanyl, which is about ten times more lipid-soluble (18). However the uptake of verapamil is most comparable in the human lung to other basic amine drugs of moderate lipid solubility such as lidocaine (60% of injected dose) (15,16) and meperidine (65% of injected dose) (18).

Diazepam represents a highly lipid-soluble drug; however, with a pKa of 3.4 it is completely unionized at physiological pH. Only 30% of the injected dose accumulated in the lung during the first pass. Such low uptake in the human lung in comparison to basic lipophilic amines such as lidocaine (15,16), propranolol (17), fentanyl (18–20), meperidine, and verapamil is consistent with animal studies. Thiopental represents another lipophilic drug (partition coefficient 102); however, it is an anionic (pKa, 7.6) barbiturate (25). Very low uptake (13.8% of injected dose) was observed with thiopental during its first pass through the human lung. Taken together the first-pass uptakes observed with verapamil, diazepam, and thiopental support the idea that a cationic amine moiety with pKa > 8.0 potentiates drug uptake in the human lung.

The mechanism of pulmonary drug uptake is not completely understood. Isolated perfused animal lung (IPL) studies have shown that accumulation of basic lipophilic drugs is flow-limited. Simple diffusion appears to be primarily responsible for translocation of these drugs from the vascular space into the extravascular space (6–14). The dependence on high lipid solubility suggests that such drugs associate with lipophilic structures (presumably lipoprotein) in lung tissue. Such lipophilic sites would necessarily include pulmonary vascular endothelial cells. The uptake curves shown in Figures 1, 2, and 3 and in our previous studies (19,20) are consistent with classical flow-limited uptake. Such uptake could be viewed as a partitioning of the drug between the blood in the vascular space and lipophilic areas in the lung. As such, the affinity of the drug for the blood (plasma protein binding) could be a factor in this partitioning.

Verapamil, diazepam, and thiopental all exhibit significant protein binding with about 90%, 97%, and 85% respectively bound to human plasma protein (14,26). However, basic drugs tend to interact primarily with alpha-acid glycoprotein, whereas albumin appears to be the major binding protein for nonbasic or acidic drugs (27–29). The high pulmonary uptake of basic amines suggests that they have a higher affinity for lipophilic sites in lung tissue than for plasma protein. For nonbasic drugs the reverse is possible. For example, diazepam uptake in the rat isolated perfused lung (IPL) is low in comparison to that of the basic lipophilic amine methadone (14). The artificial perfusate used in these studies contained 4.5% bovine serum albumin (BSA), to which diazepam is about 93% bound. If the BSA were to be omitted from the perfusate, diazepam uptake would increase about 10-fold. We concluded that diazepam binding to plasma albumin limited its availability for uptake into lung tissue. Such a mechanism may also be possible for anionic drugs such as thiopental. For example, the anionic dye indocyanine green exhibits no significant uptake in isolated dog lung lobes perfused with plasma. If a protein-free perfusate is used, extensive uptake of ICG into the lung lobe occurs (30). These results suggest that lung tissue can accumulate basic, neutral, and anionic lipophilic drugs. However, the binding of neutral and anionic lipophilic drugs to plasma albumin limits their partitioning into pulmonary tissue. Therefore, part of the dependence of extensive pulmonary drug uptake on the cationic character of the drug could be due to a difference in the binding of cationic and anionic lipophilic drugs to plasma proteins within the vascular compartment.

The role of first-pass pulmonary uptake in the plasma pharmacokinetics of verapamil, diazepam, and thiopental is not fully understood. It would primarily depend on the extent of first-pass uptake. From the 13.8% uptake of thiopental, one would predict that this nonrespiratory function of the lung is of little consequence. About one-third of the injected dose of diazepam would be sequestered in the lung during the first pass. The peak transient plasma concentrations to which other organ systems would be exposed immediately after administration would be reduced. With verapamil, one-half of the injected dose was sequestered in the lung during the first pass. In addition to resulting in peak plasma concentrations of one-half that might be expected after an intravenous bolus, a large pulmonary pool of verapamil would exist. Its influence on early verapamil plasma pharmacokinetics would be dependent on the rate at which verapamil was released from the lung

into the systemic circulation. Unfortunately, little insight into the rate at which this occurs can be obtained from the first-pass experiments. Taeger et al. estimated that 60% of the fentanyl accumulated during the first pass (80% uptake) is released back out into the circulation over the next 10 min (19). Therefore, the large pulmonary pool of basic lipophilic amines accumulated during the first pass could make a substantial contribution of the drug to the systemic circulation during the time of onset of pharmacological action.

In conclusion, the first-pass uptakes of verapamil, diazepam, and thiopental in the human lung support the idea that a high pKa of lipophilic amine drugs is one of the physicochemical factors involved in the extent of uptake. The tendency of basic lipophilic amines to become highly concentrated in lung tissue may reflect interaction of the drug with macromolecules in both the vascular and extravascular space. Finally, the first-pass uptake of verapamil in the human lung is extensive enough to suggest that this nonrespiratory function of the lung may play a role in the initial pharmacokinetics of verapamil immediately after intravenous administration. However, more insight is needed on the rate at which the large pulmonary pool of verapamil diffuses back out of the lung into the systemic circulation.

Appendix

Analytical Procedures

The first eight blood samples collected after drug injection contained no ICG or drug and were used for the construction of standard curves for quantification of the ICG and study drug by adding various amounts of the remaining injectate solution. All 1.0 mL blood samples were then diluted with 4.0 mL of water and vortexed vigorously to lyse the red cells. After centrifugation (1000 × g for 20 min), the samples were decanted into disposable cuvettes and the ICG concentration determined from absorbance at 805 nm. The samples were then frozen at −20°C until drug analysis. Diazepam and thiopental blood concentrations were determined by gas liquid chromatography (GLC), and verapamil concentrations were determined by high performance liquid chromatography (HPLC).

Diazepam determination. To 3.0 mL of the diluted blood sample, 100 μL of internal standard (flurazepam 0.15 mg/mL) was added, followed by 0.3 mL of 6 N trichloroacetic acid (TCA). The tubes were vortexed and centrifuged at 1000 × g for 20 min. The clear supernatant was transferred to a clean 10 mL conical glass centrifuge tube, and 1.0 mL of 5N sodium hydroxide (NaOH) and 200 μL of CS_2 were added. The tubes were placed on a reciprocating shaker for 10 min and centrifuged at 1000 × g for 10 min. The CS_2 formed a stable layer under the aqueous layer, and 2 μL aliquots of the CS_2 layer were injected into the GC.

The GC analyses were performed on a Hewlett Packard Model 5880 GC equipped with a flame ionization detector. The glass column (2 m long × 2 mm I.D.) was packed with 3% OV-17 on 120 mesh chromsorb W. Nitrogen (N_2) at 30 mL/min was used as the carrier gas, and the hydrogen and air flow

rates were 30 and 240 mL/min, respectively. The injector and detector temperatures were 275°C and 300°C, respectively, with an oven temperature of 260°. The absolute retention times for diazepam and flurazepam were 6.6 and 13.0 min, respectively. The lower limit of detectability for diazepam was 0.55 μg/mL of whole blood with a coefficient of variation for the method of 9.5%.

Thiopental determination. Three mL of the diluted blood sample was placed into a 5-mL vial followed by the addition of 100 μL of internal standard (inactin 0.2 μg/mL) and 200 μL of 1 N hydrochloric acid (HCl) to give a pH of 3.0. The vial was gently vortexed and the entire sample applied to 4 cm long by 0.8 cm dia. Econocolumn (Bio-Rad Laboratories, Inc.) packed with Amerlite XAD-2 resin (2 mL bed volume). The Amberlite XAD-2 (Rohm & Haas, Co.) resin had been prewashed with methanol followed by ten volumes of distilled water. The column was then washed four times with 2 mL volumes of 0.001 N HCl and the thiopental eluted with two 2.0 mL volumes of methanol into a conical glass centrifuge tube. The methanol was removed by evaporation at 40°C, the residue redissolved in 200 μL of CS_2, and 2 μL injected into the GC.

The GC analysis was carried out on a 20 m Megabore DB-5 column (J. and W. Scientific) using helium as carrier gas (15 mL/min). Separation of thiopental was achieved using a temperature program with an initial oven temperature of 160°C rising at 5°C/min to 190°C with a 5 min hold time at the final temperature. The injection port and detector temperatures were 160°C and 300°C respectively. The absolute retention times for thiopental and inactin were 4.3 min and 3.4 min, respectively. The limit of detectability was 1.2 μg/mL of whole blood and the coefficient of variation for the method was 7.5%.

For all GC analyses the ratio of area under the drug peak to its internal standard was used in comparison to the standard curves for determination for drug concentration in the 1 sec blood samples. All standard curves were linear in the concentration range studied.

Verapamil. Two mL of the diluted blood was placed in 10-mL glass screw cap tube followed by the addition of 40 μL of internal standard (verapamil analog ULFS-49, 10 μg/mL, Dr. Karl Thomae Gnbh, Biberack, FRG), 100 μl of 5 N NaOH and 5 mL of hexane:isoamyl alcohol (98.5:1.5). The tubes were mixed for 15 min on a rotary mixer, centrifuged at 1000 × g for 15 min, and the upper organic layer transferred to a clean glass tube containing 3 mL of 0.05 M H_2SO_4. This was mixed for 15 min on the rotary mixer and centrifuged at 1000 × g for 10 min. The upper hexane layer was removed by aspiration and discarded, and the aqueous layer was made basic by the addition of 100 μL of 5N NaOH followed by the addition of 5 mL of hexane: isoamyl alcohol (98.5:1.5). The tubes were mixed for 10 min on the rotary mixer and centrifuged at 1000 × g for 10 min. The upper hexane layer was transferred to a conical glass tube, centrifuged, and taken to dryness under a stream of N_2 gas at 54°C. The dried residue was redissolved in 200 μL of HPLC mobile phase, and 100 μL was injected into the HPLC.

The HPLC System consisted of a Laboratory Data Control Constametric II-G pump, Reodyne 7120 injection valve with 200 μL loop, Beckman ultrasphere ODS column (4.6 mm dia. × 25 cm long) connected to a Perkin-Elmer Model 650-10S dual monochrometer spectrophotofluorometer. The mobile phase consisted of 35% buffer (0.005 M NAH_2PO_4, 9 M sodium octyl sulfate adjusted to pH 4.6 with phosphoric acid) and 65% acetonitrile (V/V) at a flow rate of 1.5 mL/min. The excitation and emission wavelengths were 228 nm and 315 nm, respectively. All chromatograms were recorded on a Hewlett Packard Model 3390-A reporting integrator and peak height ratios of verapamil to the internal standard in comparison to the standard curve were used for quantifiation of the verapamil. Under these conditions the absolute retentions times for verapamil and internal standard were 5.10 and 10.5 min, respectively. The limit of detectability for verapamil was 5 ng/mL of whole blood with a coefficient of variation of the method of 5.6%.

Calculations. Total uptake of each drug during the first pass through the human lung was determined by comparison to the nonextractable indicator ICG (15,16,21–23). The amount of dye or drug per mL of blood was divided by the total amount of each injected and expressed as the fraction of injected drug recovered in each 1 sec arterial blood sample (Figure 1, 2, and 3). The ICG curve could be thought of as the fraction of the injected dose of drug per mL of arterial blood, had no drug extraction by the lung occurred. The difference in the area under the dye curve and the drug curve divided by the area under the dye curve is the fraction of injected drug that was extracted from the blood into the lung during the first pass. To calculate the area under the first-pass curve, the linear portion of a semilogarithmic plot of the

descending part of the curve was extrapolated to estimate the fractional concentrations had there been no recirculation. For comparative purposes, the percent of injected drug taken up into the lung was calculated at the time when 95% of the injected ICG had passed through the lung as previously described (15,16,18,20).

The instantaneous extraction ratio (ER) represents the fraction of the drug in blood taken up into the lung at each time point and was calculated as previously described (18). The cardiac output (CO) was calculated from the area under the ICG curves (18,24). Analysis of variance and Duncan's multiple range test were used for statistical comparisons.

References

1. Vane JR. The alteration or removal of vasoactive hormones by the pulmonary circulation. In: Tedeschi DH, Tedeschi RE, eds. The Importance of Fundamental Principles in Drug Evaluation. New York: Raven Press, 1968:217–35.

2. Gillis CN. Metabolism of vasoactive hormones by the rat lung. Anesthesiology 1973;39:626–32.

3. Junod AF. Uptake, release and metabolism of drugs in the lungs. Pharmacol Ther 1976;B2:511–21.

4. Anderson MW, Philpot RM, Bend JR, Wilson AGE, Eling TE. Pulmonary uptake and metabolism of chemicals by the lung. In: Duncan WAM, Leonary BS, eds. Clinical Toxicology. Amsterdam: Excerpta Medica, 1976:85–105.

5. Altiere RJ, Douglas JS, Gillis CN. Uptake and displacement of [³H] clonidine in isolated perfused rabbit lung. Biochem Pharmacol 1982;31:1039–47.

6. Orton TC, Anderson MW, Pickett RD, Eling TE, Fouts JR. Xenobiotic accumulation and metabolism by isolated perfused rabbit lungs. J Pharmacol Exp Ther 1973;186:482–97.

7. Anderson MW, Orton TC, Pickett RD, Eling TE. Accumulation of amines in the isolated perfused rabbit lung. J Pharmacol Exp Ther 1974;189:456–66.

8. Wilson AGE, Pickett RD, Eling TE, Anderson MW. Studies on the persistence of basic amines in the rabbit lung. Drug Metab Dispos 1980;7:402–24.

9. Junod AF. Mechanism of drug accumulation by the lung. In: Junod AF, Deltalles R, eds. Lung Metabolism. New York: Academic Press, 1975:214–27.

10. Wilson AGE, Law FCP, Eling TE, Anderson MW. Uptake, metabolism and efflux of methadone in "single pass" isolated perfused rabbit lung. J Pharmacol Exp Ther 1976;199:360–7.

11. Eling TE, Pickett RD, Orton TC, Anderson MW. A study of dynamics of imipramine accumulation in the isolated perfused rabbit lung. Drug Metab Dispos 1975;3:389–400.

12. Roerig DL, Dawson CA, Wang RIH. Uptake and efflux of 1-alpha-acetyl-methadol (LAAM) and methadone in the isolated perfused rat lung. Drug Metab Dispos 1982;10:230–5.

13. Roerig DL, Dawson CA, Wang RIH. Uptake of 1-alpha-acetylmethadol (LAAM) and its analgesically active metabolites, nor-LAAM and dinor-LAAM in the isolated perfused rat lung. Drug Metab Dispos 1983;11:411–6.

14. Roerig DL, Dahl PR, Dawson CA, Wang RIH. Effect of plasma protein binding on the uptake and efflux of methadone and

15. Jorfeldt L, Lewis DH, Lofstrom JB, Post C. Lung uptake of lidocaine in healthy volunteers. Acta Anaesthesiol Scand 1979; 23:567–84.

16. Jorfeldt L, Lewis DH, Lofstrom JB, Post C. Lung uptake of lidocaine in man as influenced by anaesthesia, mepivicaine infusion or lung insufficiency. Acta Anaesthesiol Scand 1983; 27:4–9.

17. Geddes DM, Nesbitt K, Trail T, Blackburn JP. First pass uptake of ¹⁴C propranolol by the lung. Thorax 1979;34:810–13.

18. Roerig DL, Kotrly KJ, Vucins EJ, et al. First pass uptake of fentanyl, meperidine and morphine in the human lung. Anesthesiology 1987;67:466–72.

19. Taeger K, Weninger E, Franke M, Finsterer U. Uptake of fentanyl by the human lung (abstract). Anesthesiology 1984; 61:A246.

20. Roerig DL, Kotrly KJ, Ahlf SB, Dawson CA, Kampine JP. Effect of propranolol on the first pass uptake of fentanyl in the human lung. Anesthesiology (in press).

21. Gillis CN, Greene NM, Cronau LH, Hammond GL. Pulmonary extraction of 5-hydroxytryptamine and norepinephrine before and after cardiopulmonary bypass in man. Circ Res 1972; 30:666–74.

22. Gillis CN, Cronau LH, Greene NM, Hammond GL. Removal of 5-hydroxytryptamine and norepinephrine from the pulmonary vascular space of man: influence of cardiopulmonary bypass and pulmonary arterial pressure on the processes. Surgery 1974;76:608–16.

23. Gillis CN, Cronau LH, Mandel S, Hammond GL. Indicator dilution measurement of 5-hydroxytryptamine clearance by the human lung. J Appl Physiol 1979;46:1178–83.

24. Guyton MD. Circulatory physiology. In: Cardiac Output and Its Regulation. Philadelphia: WB Saunders, 1963;40–70.

25. Mayer S, Maickel RP, Brodie BB. Kinetics of penetration of drugs and foreign compounds into cerebrospinal fluid and brain. J Pharmacol Exp Ther 1959;127:205–11.

26. Benet LZ, Skeiner LB. Design and optimization of dosage regimens: pharmacokinetic data. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacological Basis of Therapeutics, 7th ed, Appendix II. New York: MacMillan Pub Co, 1985:1711–3.

27. Brinkschulte B, Breyer-Pfaff U. The contribution of alpha₁ acid glycoprotein lipoproteins and albumin to the plasma binding of perazine, amitriptyline and notriptyline in healthy man. Naunyn Schmiedebergs Arch Pharmacol 1980;314:61–66.

28. Piafsky KM, Borga O. Plasma protein binding of basic drugs. II. Importance of alpha₁ acid glycoprotein for individual variation. Clin Pharmacol Ther 1977;22:545–9.

29. Piafsky KM. Disease-induced changes in the plasma binding of basic drugs. Clin Pharmacol Ther 1980;5:246–62.

30. Dawson CA, Linehan JH, Rickaby DA, Roerig DL. Influence of plasma protein on the inhibitory effects of indocyanine green and bromcresol green on pulmonary prostaglandin E₁ extraction. Br J Pharmacol 1984;81:449–55.

Hypotensive Anesthesia with Isoflurane and Enflurane during Total Hip Replacement: A Comparative Study of Catecholamine and Renin Angiotensin Responses

Jean-Marc Bernard, MD, Michel Pinaud, MD, PhD, Isabelle Maquin-Mavier, MD, Jean-Pierre Remi, MD, and Norbert Passuti, MD

Catecholamine and renin-angiotensin responses to enflurane- or isoflurane-hypotensive anesthesia were compared in a randomized study. Two groups of 10 patients undergoing total hip arthroplasty were premedicated with morphine hydrochloride (0.1 mg/kg). Anesthesia was induced with thiopental and the trachea intubated after pancuronium. Equal concentrations of each volatile agent (1.3 MAC) were administered until mean arterial blood pressure decreased to 50–60 mm Hg. Hemodynamic data and blood samples for measurements of plasma renin activity (PRA) and plasma epinephrine (E) and norepinephrine (NE) concentrations were collected 1) after induction and intubation but before the start of isoflurane or enflurane; 2) 15 min (T15) after the start of isoflurane or enflurane administration; and 3) 45 min (T45) after the start of isoflurane or enflurane administration. The desired level of hypotension was achieved at T15 with isoflurane and at T45 with both anesthetics. When hypotension was achieved, cardiac index and stroke index were significantly lower in the enflurane group while systemic vascular resistance index was lower in the isoflurane group. Increases in E and NE levels above baseline levels were significantly greater in the isoflurane group than in the enflurane group. Use of isoflurane to induce hypotension is associated with more rapid induction of hypotension, less depression of cardiac output, and better preservation of homeostatic responses than is use of enflurane.

Key Words: ANESTHESIA, ORTHOPEDIC. ANESTHETIC TECHNIQUES, HYPOTENSION— induced. ANESTHETICS, VOLATILE—enflurane, isoflurane.

Fluorinated volatile anesthetic agents are today commonly used to induce hypotension (1) and minimize bleeding during surgical procedures such as total hip replacement (2,3). Decreased blood pressure results from varying degrees of myocardial depression and peripheral vasodilation. Among fluorinated volatile anesthetic agents, isoflurane provides the best preservation of cardiac output (4). In a previous study (5), hormonal changes during isoflurane-induced hypotension for management of total hip replacement

suggested that preservation of cardiac output is due to increased sympathetic activity reflected by increased blood levels of catecholamines.

In the present study, we compared catecholamine and renin-angiotensin responses to enflurane- and isoflurane-hypotensive anesthesia during total hip replacement.

Methods

Twenty ASA physical status I or II patients (10 women and 10 men) were studied during total hip arthroplasty (Charnley Kerboull hip prosthesis). Patients were not accepted if chronically hypertensive or suffering from epilepsy or metabolic, renal, or coronary artery diseases. Those taking diuretics or betablockers or on special salt-free diets were excluded. The mean age of patients was 61 years (range

47-77). The protocol was approved by our Human Investigation Committee, and informed consent for the investigation was obtained from patients after detailed description of the procedure.

Before surgery, patients were assigned randomly and equally to one of two groups: one group was to receive isoflurane (Vaporizer: Isoflurane Vapor 19.3 Drager) and the other enflurane (Vaporizer: Enflurane Vapor 19.1 Drager) as hypotensive anesthetic agents.

Patients were premedicated intramuscularly with morphine hydrochloride (0.1 mg/kg). Anesthesia was induced with thiopental (5 mg/kg) followed by pancuronium (0.1 mg/kg). After tracheal intubation, patients were mechanically ventilated using a nonrebreathing circuit and IPPV. They received an oxygen/nitrous oxide (O_2-N_2O) mixture with FiO_2 0.5. End-tidal carbon dioxide ($Paco_2$) was monitored with a capnometer (Hewlett Packard 47210A), and initial settings were modified to maintain $Paco_2$ between 32 and 40 mm Hg with a respiratory rate of 16 /min and an I/E ratio of 1/2. No atropine was given. Either isoflurane or enflurane was started with the surgical incision. The end-tidal concentration of each fluorinated volatile anesthetic agent was monitored by an infrared analyzer (Normac Datex). Equal concentrations (1.3 MAC) were administered until mean arterial blood pressure (MAP) decreased to 50-60 mm Hg. This MAC level (1.3) was selected because it is commonly used in our practice for production of deliberate hypotension during total hip replacement. Concentrations were modulated to avoid more pronounced hypotension.

Throughout anesthesia, heart rate (HR) was monitored by a V5 electrocardiogram (ECG) lead. A Teflon cannula was inserted into the radial artery for systolic (SAP) and diastolic (DAP) blood pressure measurements. A 7-Fr triple-lumen thermodilution catheter was inserted through the right jugular vein to measure right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured by thermodilution using iced injectate in triplicate. All pressures were referenced to the level of the right atrium. HR and pressures were recorded simultaneously on a polygraph (Mingograf 803 Siemens Elema). Po_2, pH, Pco_2, and hemoglobin (Hb) concentration (ABL 300 Acid-base analyzer Radiometer), and Hb saturation (So_2) (OSM2 Hemoximeter Radiometer) were measured in arterial and mixed venous blood. Derived values such as MAP, cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVRI), arterio-venous difference in O_2 contents ($C(a-\bar{v}O_2)$) and oxygen consumption

index ($\dot{V}o_2I$) were computed according to standard formulae (6).

Fluid replacement was done with polygeline to maintain PCWP ≥ 4 mm Hg, to provide sufficient ventricular preload, and to avoid deleterious consequences of hypovolemia. Polygeline (Plasmion®) is an oncotically active gelatine with molecular weights between 30,000 and 40,000. Ten minutes after completion of a 500-mL infusion, the average volume expansion was 550 mL; it has an effective half-life of 4 to 6 hr. Blood replacement (red blood cells) was begun when blood loss exceeded 300 mL. Operative blood loss was assessed by weighing sponges, measuring suction drainage, and estimating the amount of blood in the area of the wound. This was determined blindly by nurses unaware of which agent was being used. During the first postoperative day the blood collected from wound drainage was measured.

Arterial blood samples were drawn for determination of plasma renin activity (PRA) and plasma catecholamine levels. PRA was measured by the method of Haber et al. (7) using an angiotensin I radioimmunoassay kit (SB-REN-1 CEA SORIN). Norepinephrine (NE) and epinephrine (E) plasma concentrations were measured with a double-isotope enzymatic assay with a sensitivity of 1.5 pg/mL for both E and NE (8). The coefficients of variation were 3.2% and 3.5% for NE and E, respectively (intraassay), and 4.3% and 4.4% (interassay).

Hemodynamic data and blood samples for measurements of PRA, NE, and E were collected at three times: 1) baseline samples (B) were obtained when the patient was in the lateral position after induction and intubation and before the start of isoflurane or enflurane; 2) 15 min (T15) after the start of isoflurane or enflurane administration; and 3) 45 min (T45) after the start of isoflurane or enflurane administration. These times were selected because they would represent relatively stable conditions before the start of major orthopedic trauma including femoral bone drilling or cement insertion.

All results are expressed as mean ± SEM. Comparisons were made by analysis of variance for repeated measurements, when the two factors were treatment (isoflurane or enflurane) and time (before and during anesthesia), followed by t-tests with Bonferroni corrections. Statistical analysis of plasma renin activity and plasma catecholamines was done after logarithmic transformation of the data. Unpaired t-tests were used to compare blood loss, fluid replacement, postoperative hematocrits, and postoperative hemoglobin concentrations. Statistical significance was assumed for $P < 0.05$.

Table 1. Procedure Summary

	Isoflurane Group (N = 10)	Enflurane Group (N = 10)
Age (yr)	60.7 ± 3.1	61.9 ± 3.1
Weight (kg)	70.9 ± 6.6	63.5 ± 4.3
Sex Ratio	6M;4F	4M;6F
Duration of Anesthesia (min)	86 ± 6.9	83 ± 6.3
Blood Loss (mL)		
during operation	250 ± 31	270 ± 34
1st postoperative day	280 ± 43	280 ± 45
Transfusions (number of patients)		
no units	2	2
one unit	4	5
two units	3	2
three units	1	1
IV Infusions (mL)		
polygeline	1070 ± 70	1030 ± 100
Postoperative Hematocrit (%)	36.1 ± 1.4	36.4 ± 1.2
24th Postoperative Hour Hemoglobin (g/dL)	12.3 ± 0.3	12.4 ± 0.3

All values are mean ± SEM; unpaired t-test NS.

Results

No differences were observed between the two groups with respect to age, sex, weight, surgical procedure, and blood loss. Cumulative volumes of polygeline and red blood cells administered were not different, regardless of the hypotensive agent used (Table 1).

Hemodynamic results are summarized in Table 2. E, NE, and PRA data are shown in Figure 1.

In the isoflurane group, MAP was significantly decreased at T15 and T45. Hypotension was associated with significant decreases in SVRI at T15 and T45. CI, SI, and Vo_2I did not change significantly. E, NE, and PRA levels increased significantly. There were no complications during and after the study in this group.

In the enflurane group, MAP was not significantly decreased until T45. CI, SI, and Vo_2I were, nevertheless, significantly below baseline levels at both T15 and T45. E and PRA levels increased significantly, but NE levels did not. In one patient, undesirable hypotension (MAP = 49 mm Hg) related to moderate bleeding (bone resection) occurred with a low CI (1.5 $L\cdot min^{-1}\cdot m^{-2}$). Despite discontinuation of enflurane administration and adequate fluid replacement, CI remained low during 20 min. In this patient, PRA, E, and NE were, respectively, 0.6 $ng\cdot mL^{-1}\cdot hr^{-1}$, 21 pg/L, 721 pg/L at B; 0.7 $ng\cdot mL^{-1}\cdot hr^{-1}$, 25 pg/L, 650 pg/L at T15; and 0.6 $ng\cdot mL^{-1}\cdot hr^{-1}$, 36 pg/L, 680 pg/L at T45. This patient did not suffer from long- or short-term adverse effects due to the low cardiac output.

Variations in MAP were similar in both groups. The isoflurane and enflurane groups, though with similar baseline data, were significantly different in certain respects: CI at T45, SI at T45, and Vo_2I at T15 were lower in the enflurane group; SVRI was lower in the isoflurane group at T15 and T45; E and NE at T15 and at T45 were higher in the isoflurane group.

Discussion

Isoflurane and enflurane, both accompanied by the same degree of bleeding during and after surgery, provided equally satisfactory operating conditions. However, the mechanisms underlying decreases in arterial blood pressure differed. With isoflurane, which led to arterial vasodilation and did not change cardiac index, the 50–60 mm Hg level of mean arterial blood pressure was obtained rapidly. This could be attributed to the lower blood/gas solubility coefficient of this agent (4). In the enflurane group, hypotension, due to a marked depression of myocardial contractility, took more than 15 min to achieve. However, the decrease in cardiac output was accompanied by a significant decrease in oxygen consumption induced by enflurane. The absence of increase in oxygen extraction suggests that oxygen delivery was adequate in the enflurane group. In both groups cardiac output remained adapted to peripheral oxygen demand as indicated by the absence of changes in arterio-venous differences in oxygen content and in oxygen extraction ratios. In contrast to the decrease seen with enflurane, the isoflurane-induced hypotension, not accompanied by a decrease in oxygen consumption, might create a potentially hazardous metabolic situation if a further decrease in arterial blood pressure were to occur for any reason. In fact, such a situation would require stopping the fluorinated volatile anesthetic agent in order to increase blood pressure and ensure the perfusion of vital organs.

Substantial depression of blood pressure occurred during enflurane administration, but only plasma epinephrine, not norepinephrine levels increased significantly above baseline values. Our results are in agreement with the findings of Skovsted and Price (9), which show that, experimentally, sympathetic activity during enflurane anesthesia is depressed, suggesting that cardiovascular depression results at least partly from blunted responsiveness to increases in sympathetic tone. Our results show that isoflurane anesthesia in the presence of the same level of decreased blood pressure, was associated with significant increases in plasma epinephrine and norepinephrine levels above baseline values; these increases

Table 2. Comparison of Hemodynamic Variables before (B) and 15 min (T15) and 45 min (T45) after Starting Isoflurane (I) or Enflurane (E)

		Before Hypotension (B)	T15	T45	Intragroup ANOVA P Value
RAP (mm Hg)	I	2.3 ± 0.7	2.4 ± 0.5	2.1 ± 0.5	NS
	E	1.8 ± 0.4	3.4 ± 0.7	2.4 ± 0.7	NS
PCWP (mm Hg)	I	6.1 ± 0.6	6.9 ± 0.9	6.4 ± 0.5	NS
	E	5.2 ± 0.7	8.2 ± 1.0	6.4 ± 0.7	NS
MAP (mm Hg)	I	82.4 ± 2.8	60.7 ± 3.7***	58.1 ± 2.6****	<0.001
	E	83.1 ± 3.5	74.8 ± 4.2	58.6 ± 2.0****	<0.001
HR (beats/min)	I	82.4 ± 3.7	80.5 ± 3.7	80.3 ± 3.6	NS
	E	79.4 ± 2.9	79.0 ± 3.5	76.1 ± 3.9	NS
CI $(L \cdot min^{-1} \cdot m^{-2})$	I	2.70 ± 0.20	2.65 ± 0.26	2.71 ± 0.30	NS
	E	2.77 ± 0.14	2.09 ± 0.10***	1.93 ± 0.11•***	<0.001
SI $(mL \cdot beat^{-1} \cdot m^{-2})$	I	34.0 ± 2.3	33.0 ± 2.9	33.8 ± 3.3	NS
	E	34.9 ± 2.3	26.3 ± 1.2**	22.8 ± 2.3••***	<0.001
SVRI $(dyn \cdot sec \cdot cm^{-5} \cdot m^{-2})$	I	2379 ± 168	1772 ± 186*	1668 ± 136**	<0.02
	E	2402 ± 169	2684 ± 256•	2352 ± 165•••	NS
$C(a-\bar{v})o_2(mLO_2/dL)$	I	3.20 ± 0.16	3.42 ± 0.28	3.23 ± 0.23	NS
	E	3.31 ± 0.14	3.22 ± 0.25	3.48 ± 0.26	NS
$\dot{V}o_2I$ $(mLO_2 \cdot min^{-1} \cdot m^{-2})$	I	87.7 ± 5.8	87.9 ± 6.8	81.6 ± 5.8	NS
	E	90.6 ± 4.5	68.5 ± 4.9*	68.0 ± 5.3	<0.01
O_2ER (%)	I	18 ± 0.6	20 ± 1.6	19 ± 0.9	NS
	E	20 ± 0.9	19 ± 1.3	22 ± 1.6	NS

All values are mean ± SEM.
*$P < 0.05$; **$P < 0.02$, ***$P < 0.01$, ****$P < 0.001$ when compared with before hypotension values; •$P < 0.05$, ••$P < 0.02$, •••$P < 0.001$, when compared with isoflurane group values.
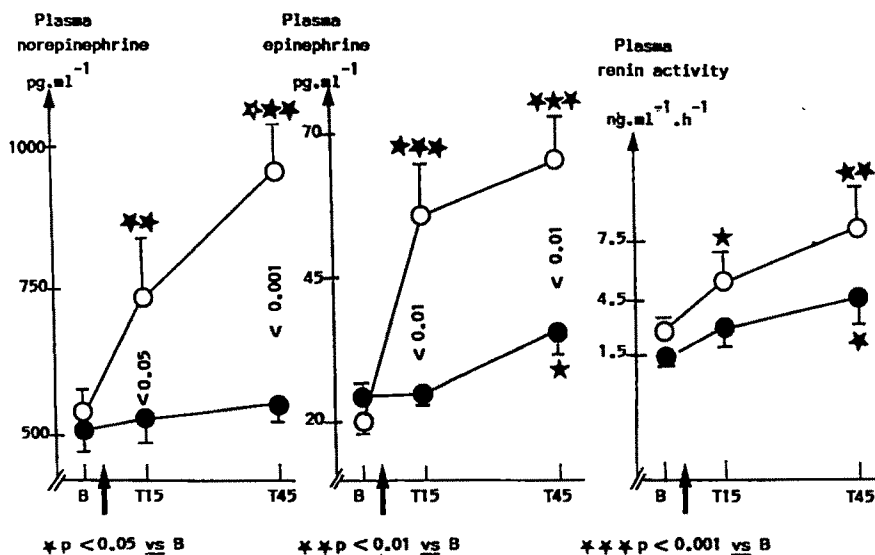
Figure 1. Plasma catecholamine levels and renin activity before (B), 15 min (T15) and 45 min (T45) after starting (↑) isoflurane (O) and enflurane (●).

were greater than those seen during equal levels of enflurane hypotensive anesthesia. These results do not corroborate the observation by Roizen et al. (10) that the doses of fluorinated volatile agent blocking adrenergic responses in 50% of unpremedicated individuals to a skin incision (MAC-BAR) were 1.45 ± 0.08 MAC with halothane and 1.60 ± 0.13 MAC with enflurane. It is not clear in our study why isoflurane, a more potent anesthetic than enflurane (4), led to

greater plasma epinephrine and norepinephrine levels with equi-MAC concentrations.

Concerning the possible role of surgical stress in our study, care was taken to assure that all operations were performed by the same surgeon (NP) and during at the same times in the morning (8–11 hr). Baseline data were collected after tracheal intubation and before skin incision, at T15 (after muscle dissection) after surgical drapes had been placed around

the wound, and at T45, after femoral head removal but before insertion of and cementing of the prosthesis. If surgical stress was a factor in increased plasma catecholamine levels, it did not cause the neuroendocrine differences observed between the two groups anesthetized at equi-MAC concentrations. There may have been a discrepancy between the anesthetic dose and the absolute change in plasma catecholamine levels (because of different sites of anesthetic blocking action for each or different site sensitivities) (10). Likewise, we carefully maintained PCWP at a minimal level of 4 mm Hg to avoid hypovolemia, even though PCWP did not reflect the exact magnitude of volemia because of myocardial depression. However, if hypovolemia occurred and stimulated the sympathetic nervous system independently (11), this mechanism was less likely to have been involved during isoflurane than during enflurane since the latter led to myocardial depression and did not account for neuroendocrine intergroup differences.

Our results suggest that the effect of enflurane and isoflurane on sympathetic tone may differ during equihypotensive and equi-MAC anesthesia, which would be in agreement with the results of Kortly et al. (12), who found that arterial baroreflex depression was less pronounced during isoflurane than during enflurane or halothane anesthesia. The fact that HR was unchanged and similar in our two groups, despite hypotension, may be explained by age impairment on the baroreflex function (13) or by premedication. In patients given isoflurane, the tendency for HR to increase without morphine and decrease with morphine suggests that such premedication decreases HR during anesthesia and surgery (14).

Experimentally, PRA does not increase when arterial blood pressure is lowered (to 30% of the control values) during enflurane anesthesia (15). However, through use of saralasin—a competitive inhibitor of angiotensin II—a significant role for maintenance of blood pressure by the renin-angiotensin system during enflurane anesthesia has been demonstrated (15). Persistent renin response to additional decreases in blood pressure induced by nitroprusside is observed despite enflurane inhalation (16). Our data on PRA levels in the enflurane group are in agreement with these experimental results. However, renin response was similar in both groups and greater catecholamine release did not potentiate renin-angiotensin responses (17) to decreases in blood pressure in the isoflurane group.

Poor preservation of homeostatic responses to hypotension, including catecholamine levels and PRA, may be disadvantagous during hypotensive enflurane anesthesia. In some clinical situations, such as operative difficulties and unpredictable bleeding, hypovolemia may be poorly tolerated during enflurane (and even after its discontinuation). Horan et al. (18) found the combination of enflurane (1 MAC) and 20% hypovolemia to be particularly deleterious to the circulation in the presence of a decrease in CO and an increase above normal range in arteriovenous difference in oxygen contents $(C(a-\bar{v}O_2) = 7.8 \pm 2$ mL%). This is in agreement with the results of Weiskopf et al. (19) in studies of dogs in which—in response to a withdrawal of 20% and 30% of blood volume—CO was maintained at a significantly lower level during enflurane (1.15 MAC) than during equipotent isoflurane concentrations. The adrenergic response to hypovolemia during isoflurane anesthesia (1 MAC) is not altered by infusions of propranolol (0.3 mg/kg), whereas in the same experimental conditions enflurane (1 MAC), propranolol, and a withdrawal of 20% of blood volume are poorly tolerated $(C(a-\bar{v}O_2) = 9.8$ mL%) with enflurane (20). This suggests that relative preservation of homeostatic response to hypovolemia is more marked during isoflurane anesthesia than during enflurane anesthesia, since the same doses of propranolol may have slight and strong effects on sympathetic response to hypovolemia during isoflurane and enflurane anesthesia, respectively. Therefore, two explanations for better hemodynamic tolerance to hypovolemia during isoflurane may be proposed: a less marked depression of myocardial contractility with isoflurane than with enflurane (20); and a lower blood/gas solubility coefficient with isoflurane than with enflurane (4), providing more rapid elimination and hence better and more prompt responses to operative difficulties such as unpredictable bleeding.

In conclusion, clinical use of enflurane hypotensive anesthesia is associated with less significant catecholamine release than occurs with isoflurane under the same conditions. Isoflurane seems to be more appropriate than enflurane for induction of hypotensive anesthesia.

References

1. Cottrell JE. Is deliberate hypotension a useful clinical technique in 1987? In: Annual Refresher Course Lectures, American Society of Anesthesiologists, no. 331, 1987:1–7.

2. Thompson GE, Miller RD, Stevens WC, Murray WR. Hypotensive anesthesia for total hip arthroplasty. A study of blood loss and organ function (brain, heart, liver, and kidney). Anesthesiology 1978;48:91–6.

3. Bernard JM, Pinaud M, Ganansia MF, Chatelier H, Souron R, Letenneur J. Systemic haemodynamic and metabolic effects of deliberate hypotension with isoflurane anaesthesia or sodium nitroprusside during total hip arthroplasty. Can J Anaesth 1987;34:135–40.

4. Eger EI II. The pharmacology of isoflurane. Br J Anaesth 1984;56:71S–99S.

5. Bernard JM, Pinaud M, Macquin-Mavier I, Remi JP, Souron R, Bainvel J. Impact of surgical stress on the haemodynamic profile of isoflurane-induced hypotension. Acta Anaesthesiol Scand 1988;32:248–52.

6. Hug CC jr. Monitoring. In: Miller RD, ed. Anesthesia. New York, Churchill Livingstone Inc, 1986:411–63.

7. Haber E, Koerner T, Page LB, Kimura B, Purnode A. Application of radio-immunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J Clin Endocrinol 1969;29:1349–55.

8. Brown MJ, Jenner DA. Novel double-isotope technique for enzymatic assay for catecholamine permitting high precision, sensitivity and plasma sample capacity. Clin Sci 1981;61:591–8.

9. Skovsted P, Price HI. The effects of ethrane on arterial pressure, preganglionic sympathetic activity and barostatic reflexes. Anesthesiology 1972;36:257–62.

10. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MACBAR. Anesthesiology 1981;54:390–8.

11. Halter JB, Pflug AE, Porte D jr. Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 1977;45:936–44.

12. Kortrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9.

13. Duke PC, Wade JG, Hickey RF. The effects of age on baroreceptor reflex function in man. Can Anaesth Soc J 1976;23:111–24.

14. Cahalan MK, Lurz FW, Eger EI II, Schwartz LA, Beaupré PN, Smith JS. Narcotics decrease heart rate during inhalational anesthesia. Anesth Analg 1987;66:166–70.

15. Miller ED, Longnecker DE, Peach MJ. The regulatory function of the renin-angiotensin system during general anesthesia. Anesthesiology 1978;48:399–403.

16. Miller ED jr, Ackerly JA, Vaughan ED jr, Peach MJ, Epstein RM. The renin-angiotensin system during controlled hypotension with sodium nitroprusside. Anesthesiology 1977;47:257–62.

17. Davis JO, Freeman RH. Mechanisms regulating renin release. Physiol Rev 1976;56:1–56.

18. Horan BF, Prys-Roberts C, Hamilton WK, Roberts JG. Haemodynamic responses to enflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol. Br J Anaesth 1977;49:1189–97.

19. Weiskopf RB, Townsley MI, Riordan KK, Chadwick K, Baysinger M, Mahoney E. Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane and ketamine anesthesia. Anesth Analg 1981;60:481–91.

20. Horan BF, Prys-Roberts C, Roberts JG, Bennett MJ, Foex P. Haemodynamic responses to isoflurane anaesthesia and hypovolaemia in the dog, and their modification by propranolol. Br J Anaesth 1977;49:1179–87.

Effect of Various Propofol Plasma Concentrations on Regional Myocardial Contractility and Left Ventricular Afterload

André Coetzee, MB, ChB, FFA, MMed, FFARCS, PhD, MD, Pieter Fourie, BSc, MB, ChB, PhD, Johan Coetzee, BSc, MB, ChB, MMed, Emmerentia Badenhorst, NDT, Aart Rebel, BIng, Chris Bolliger, MD, Reinhardt Uebel, BPharm, MSc, Cheryllynne Wium, MSc, and Carl Lombard, PhD

COETZEE A, FOURIE P, COETZEE J, BADENHORST E, REBEL A, BOLLIGER C, UEBEL R, WIUM C, LOMBARD C. Effect of various propofol plasma concentrations on regional myocardial contractility and left ventricular afterload. Anesth Analg 1989;69:473–83.

The cardiovascular effects of propofol infusions, designed to maintain constant plasma concentrations, were examined in an open-chested pig model. Regional myocardial contractility was measured with the end-systolic pressure-length relationship (E_{es}) and left ventricular afterload quantified by the effective arterial elastance (E_a). The propofol plasma concentrations in this study varied between 0 and 7.73 (SEM 0.96) µg/mL. A significant correlation for the increasing propofol plasma concentration and a decrease in myocardial contractility (P = 0.0056) was demonstrated, and the E_a remained constant. This gave rise to a reduction in stroke volume (P = 0.002) and, combined with a decrease in the heart rate (P = 0.0001), led to a reduction in the cardiac output (P = 0.0001). When the propofol infusion was stopped, myocardial contractility did not recover in parallel with the decrease in plasma propofol concentration.

Key Words: ANESTHETICS, INTRAVENOUS—propofol. HEART, MYOCARDIAL FUNCTION—propofol.

Propofol (2,6 di-isopropyl phenol) (Diprivan, Stuart) has pharmacokinetic characteristics suitable for use as a total intravenous anesthetic agent (1). Numerous publications indicate that propofol administration is associated with decreases in blood pressure, systemic vascular resistance, cardiac output (CO), and stroke volume (SV) (2–7). The effect of propofol on myocardial contractility and left ventricular (LV) afterload has, however, not been completely quantified. This study therefore posed the following questions: (1) Does propofol affect myocardial contractility? and (2) Do propofol infusions affect LV afterload?

Methods

Approval from the Ethics Committee of the Faculty of Medicine, University of Stellenbosch, was obtained for these studies. Animal care conformed to national and institutional guidelines.

Initially, three pigs, each subjected to the same anesthetic technique described below, received an intravenous dose of propofol 2.5 mg/kg during 20 sec. Subsequent propofol plasma concentrations were used to calculate the pharmacokinetic model upon which we based the dosage strategy for the main study. (Appendix A).

There were eight pigs in the main study (mean mass 25 kg). Anesthesia was induced with intravenous thiopental 4–6 mg/kg. A tracheostomy was performed, the trachea intubated, and the animals ventilated with nitrogen (70%) and oxygen (30%) with a pressure cycled ventilator and circle system (fresh gas flow = 3 L/min) equipped with a carbon dioxide absorber. Fractional Inspiratory Oxygen (FI_{O_2}) was monitored with an oxygen analyzer (Servo Gas Monitor, Siemens). Muscle relaxation was ob-

tained using pancuronium 0.1 mg/kg and was maintained by means of a constant infusion of 0.10 $mg \cdot kg^{-1} \cdot hr^{-1}$. $Paco_2$ was maintained between 36.0 and 38.3 mm Hg by adjusting the tidal volume and ventilation frequency when necessary.

Anesthesia was maintained using 0.7% halothane in the inspired gas mixture for the duration of the surgical manipulations. Thereafter the concentration was reduced to 0.3% for the remainder of the experiment using a calibrated halothane vaporizer with continuous monitoring of end-tidal halothane concentration (Servo Gas Monitor). No surgical or other procedures were carried out at the low halothane concentration.

Body temperature, measured with the thermistor at the tip of a pulmonary artery (PA) catheter, was maintained between 36.8° and 37.2°C with the aid of an undertable heating system. Normal saline, 5 mL· $kg^{-1} \cdot hr^{-1}$ was infused throughout the experiment.

A catheter was inserted into the carotid artery, using a lateral neck incision and positioned with its tip lying within 1 cm of the aortic valve. The catheter was connected to a transducer (Statham P_{23}, natural frequency 50.3 Hz) for the measurement of (central) arterial blood pressure. A PA catheter (Edwards Lab) was floated into the proximal PA. The position of the catheter was confirmed after the chest was opened, and at postmortem dissection it was verified that the proximal port of the catheter was in the right atrium. Cardiac output (CO) was measured in triplicate using a CO computer (Mansfield 9530) with manual injection of 5 mL of a 5% dextrose (at 0°C) into the proximal port of the catheter.

Both femoral arteries were dissected, and through one an occlusion balloon catheter (Edwards Lab, size 8/14 F) was inserted into the descending aorta. The balloon was used to increase left ventricular (LV) afterload during five to eight consecutive heartbeats to obtain end-systolic pressure-length points for the construction of the end-systolic pressure-length relationship (E_{es}).

A microtip flow transducer (Millar Instruments) was inserted through the other femoral artery with the tip of the catheter lying 0.5 to 1 cm distal to the aortic valve. The position of the catheter was also verified when the chest was opened and confirmed at postmortem dissection. SV was calculated from CO and heart rate (HR) and, as SV is equal to the area under the velocity signal recorded by the microtip catheter, the computer calculated aortic blood flow and acceleration.

A thoracotomy and pericardectomy were performed and the heart suspended in a pericardial cradle without obstructing venous inflow. A 16-gauge cannula, connected to a pressure transducer
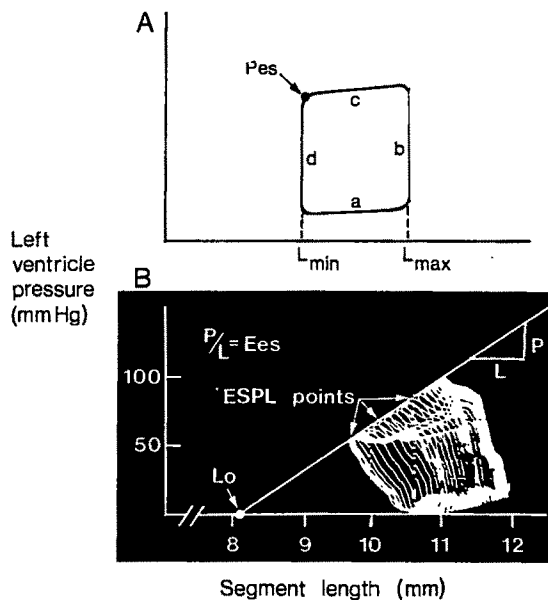
Figure 1. (a) A LV pressure-length (P-L) loop. a = diastolic filling, b = isovolemic contraction, c = ejection of the SV, d = isovolemic relaxation, L_{max} = segment length at the end of diastole, L_{min} = segment length at the end of systole, and Pes = LV pressure at end-systole. (b) Consecutive LV beats against an increasing afterload. Each loop represents a single beat. The various end-systolic pressure-length points obtained were used tc construct the end-systolic pressure-length (ESPL) relationship (E_{es}). The slope of the line E_{es} is a load-independent index of regional myocardial contractility. L_0 is the segment length at the time LV pressure is zero.

(Statham P_{23} Db; natural frequency 50.6 Hz), was inserted into the LV to measure LV pressure and record left ventricular end-diastolic pressure (LVEDP) from a magnified calibration. A computer calculated HR from the LV pressure signal.

Two piezo-electric crystals were inserted into the LV subendocardium, 1 to 1.5 cm from the left anterior descending (LAD) coronary artery, perpendicular to the base-apex axis of the heart. This was used to measure segmental length (Schuessler and Associates) during the cardiac cycle (8). The maximum segment length (L_{max}) is the distance between the crystals at the beginning of the sharp up slope of the LV pressure signal, and the minimum length (L_{min}) is the distance between the crystals at the time of aortic valve closure. The difference (dL) between maximum and minimum length represents systolic segmental shortening (dL = $L_{max} - L_{min}$) and this was normalized for L_{max} and expressed as a percentage (dL% = $dL/L_{max} \cdot 100$).

LV pressure and segmental length signals were combined on an oscilloscope (Tectronix S103N), which allowed for the recording of the LV pressure-length loop for every heartbeat (Figure 1). Standard calibrations were used throughout.

Arterial blood gas tensions, pH, and hemoglobin levels were measured at hourly intervals with an automated blood gas analyzer (Corning).

The pressure transducers were calibrated before and during the experiments using a mercury manometer. Signals were recorded on paper (Beckman) 5 sec after disconnection of the tracheostomy tube from the ventilator. Signals were also digitized (ADA converter, Central Electronic Services, University of Stellenbosch) and a microcomputer (Olivetti M24 with 640 kilobytes random-access memory and 8087 numeric coprocessor) stored data directly on floppy diskettes. The data were sampled at 200 Hz for 5 sec.

A computerized compressed spectral array electroencephalographic (EEG) monitor continuously monitored cerebral activity.

Calculations

1. General cardiovascular parameters.

The computer calculated mean arterial pressure (MAP) using the area under the aortic pressure curve. End-systolic pressure (Pes) was recorded from the LV at aortic valve closure. Maximal segmental LV time-varying elastance, i.e., E_{es}, was calculated from the series of pressure-length (PL) loops recorded on inflating the intra-aortic balloon to increase LV afterload (Figure 1). The computer selected the maximum pressure-length ratio for each of these afterloaded beats and performed a linear regression (least-squares method) on the points obtained. The slope of this regression is expressed in units of mm Hg/mm and is an indication of segmental myocardial contractility (9–11). The intercept of E_{es} on the abcissa, L_0(mm), indicates LV segmental length at the time LV pressure is zero (Figure 1).

The hydraulic impedance of the aorta was modelled using the Windkessel model (12,13). From this model, the effective arterial elastance (E_a) was calculated. This is a lumped characterization of the arterial impedance which also incorporates the influence of the heart rate:

$$E_a = (Ro + Rp)/[ts + \tau (1 - exp^{-td/\tau})] \qquad (1)$$

where Ro = characteristic impedance, Rp = peripheral resistance, ts and td = systolic and diastolic times of a cardiac cycle, and τ = time constant of the diastolic pressure curve (assuming a monoexponential decay) (14). The time constant was calculated from the expression

$$\tau = RpC = td(lnPes - lnDAP) \qquad (2)$$

where Pes = end-systolic arterial pressure, DAP = diastolic arterial pressure, and C = capacitance.

2. Pharmacokinetic model.

Arterial blood concentrations of propofol were determined at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 30, 45, 60, 90, 120, 180, 210, and 240 min after injection of 2.5 mg/kg propofol intravenously into three animals. A computer program, employing conventional back projection ("stripping") techniques, calculated the approximate parameters for the "biexponential" expression of the form

$$Cp = Ae^{-\alpha t} + Be^{-\beta t} \qquad (3)$$

where C_p = concentration (μg/mL) and t = time (min). These parameters were used by an iterative nonlinear least-squares regression curve fitting computer program to obtain the expression with the best fit for each pig (Appendix A). The algorithm employed was based on the program described by Nielsen-Kudsk (15) employing the Akaike (16) information criterion as an indicator of good fit (17). From parameters thus obtained, the constants for an open mammillary two-compartment pharmacokinetic model for each pig were determined using conventional pharmacokinetic theory (18,19). Results from this limited number of animals were used only as a guideline for the propofol infusion and should not be confused with in-depth kinetic data.

Determination of the Plasma Concentrations of Propofol

Two mL of blood was withdrawn from the right atrium using new 2 mL syringes, placed in vacuum siliconized tubes, and sent to the laboratory where the red blood cells were immediately separated from the serum by centrifugation. Propofol was thereafter measured in serum by liquid chromatography. A Shimadzu LC-4A chromatograph was coupled to an electrochemical detector (ESA Coulochem 5100A) and serum samples (25 μL) were injected through a manual valve system onto an online reverse phase precolumn extraction system (RSA patent application 880313). The sample was introduced onto an analytical column (C$_8$ Brownlee 10 cm 3 μ) by manual valve switching. Isocratic elution was carried out with 55% organic phase in 0.05 M phosphate buffer (pH 4.0). The organic phase consisted of 8:2 acetonitrile and isopropanol while detection of the propofol was done between 0.4 and 0.5 mV. Complete elution of each injected sample was obtained in about 5 min. A standard curve was prepared for each batch of samples analyzed in any one day to correct for changes in the sensitivity of the detector. After 4 days of use, the

Table 1. General Hemodynamic Data, Segmental Contractility (Ees) and Effective Arterial Elastance (Ea) during the Increase in Blood Propofol Concentrations

Propofol blood concentration (μg/mL)	HR (bpm)	MAP (mm Hg)	Pes (mm Hg)	LVEDP (mm Hg)	SV (mL)	CO (L/min)	L_{max} (mm)	dL (mm)	dL% (%)	$-dp/dt_{max}$ (mm Hg/sec)	Ees (mm Hg/mm)	L_0 (mm)	Ea (mm Hg/mL)	Ro (mm Hg·sec^{-1}·mL^{-1})	Rp (mm Hg·sec^{-1}·mL^{-1})	C (mL/mm Hg)
0.00	117.01 ±3.60	84.39 ±4.22	85.51 ±4.66	10.69 ±1.13	26.85 ±1.59	3.14 ±0.20	10.98 ±0.79	2.31 ±0.33	20.42 ±1.97	−1286.13 ±75.16	83.98 ±20.02	7.48 ±0.40	3.48 ±0.25	0.15 ±0.03	1.57 ±0.14	0.71 ±0.07
1.08 ±0.17	113.96 ±4.33	84.50 ±3.65	85.58 ±3.68	10.94 ±1.00	26.85 ±0.82	3.07 ±0.17	10.92 ±0.79	2.32 ±0.32	20.62 ±1.74	−1294.10 ±62.84	78.49 ±19.57	7.12 ±0.40	3.46 ±0.18	0.16 ±0.04	1.56 ±0.10	0.78 ±0.10
1.77 ±0.21	113.30 ±4.67	84.84 ±3.43	85.89 ±3.03	11.75 ±0.80	26.90 ±1.41	3.06 ±0.24	10.98 ±0.77	2.31 ±0.30	20.68 ±1.60	−1251.50 ±68.54	72.40 ±18.13	7.09 ±0.36	3.49 ±0.25	0.18 ±0.05	1.58 ±0.14	0.84 ±0.12
2.69 ±0.39	113.99 ±5.39	82.95 ±3.27	86.02 ±3.38	11.31 ±0.86	26.41 ±1.45	3.02 ±0.24	10.85 ±0.81	2.24 ±0.29	20.01 ±1.50	−1305.64 ±61.60	71.90 ±12.76	7.16 ±0.43	3.43 ±0.24	0.19 ±0.05	1.54 ±0.13	0.90 ±0.17
3.90 ±0.53	110.71 ±4.43	82.90 ±4.62	86.53 ±3.53	11.88 ±1.08	24.89 ±1.33	2.76 ±0.21	10.89 ±0.82	2.23 ±0.28	19.89 ±1.50	−1310.64 ±67.10	52.54 ±12.09	6.00 ±0.57	3.70 ±0.35	0.19 ±0.06	1.72 ±0.17	0.77 ±0.13
5.27 ±0.76	107.74 ±3.88	84.31 ±4.12	85.98 ±4.29	11.00 ±1.24	24.76 ±0.94	2.69 ±0.17	10.91 ±0.82	2.07 ±0.27	18.45 ±1.42	−1287.53 ±56.21	43.81 ±7.93	6.36 ±0.59	3.77 ±0.28	0.19 ±0.05	1.79 ±0.16	0.78 ±0.16
6.76 ±0.88	108.19 ±3.49	83.60 ±4.81	84.99 ±4.72	10.98 ±1.33	24.96 ±0.85	2.70 ±0.13	10.85 ±0.79	2.01 ±0.25	18.02 ±1.29	−1260.21 ±50.21	41.16 ±9.76	5.69 ±0.66	3.72 ±0.27	0.18 ±0.06	1.78 ±0.14	0.78 ±0.11
6.99 ±0.91	108.56 ±3.81	83.83 ±5.43	85.47 ±5.01	11.71 ±1.06	25.13 ±1.40	2.71 ±0.13	11.03 ±0.89	2.07 ±0.25	18.32 ±1.14	−1271.73 ±77.35	37.61 ±9.72	5.56 ±0.80	3.75 ±0.36	0.20 ±0.07	1.75 ±0.19	0.78 ±0.12
7.73 ±0.94	110.31 ±3.91	84.34 ±5.21	87.53 ±4.32	13.43 ±0.97	24.10 ±1.17	2.65 ±0.14	11.03 ±0.90	2.02 ±0.25	17.81 ±1.08	−1263.65 ±81.65	43.14 ±9.90	6.61 ±0.78	3.94 ±0.63	0.18 ±0.06	1.82 ±0.32	0.90 ±0.23

Values are X ± sem for eight animals. The abbreviations are similar to those used in the text, and statistically significant correlations between propofol blood concentration and hemodynamic parameter are discussed in the text.

Figure 2. The E_{es} for eight experiments in which the blood concentration of propofol was increased by constant infusion. There was a significant inverse correlation between the blood concentration of propofol and E_{es}. From the figure it would appear as if the E_{es} for all but one of the animals decreased when the propofol blood concentration exceeded 2.4 $\mu g/mL$.
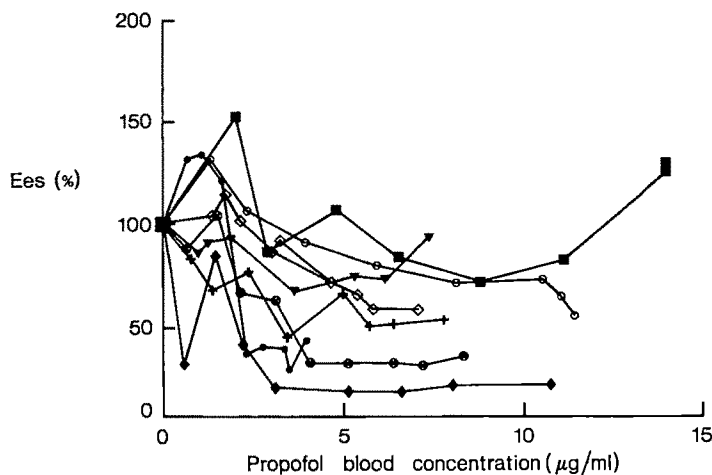
detector was polished according to the instructions of the manufacturer, which restored its sensitivity to that of day 1.

Experimental Protocol

After completion of surgery, end-tidal halothane concentration was reduced to 0.3%, and the animals were left undisturbed for 45 min to obtain a pharmacologic steady state. Thereafter blood samples were drawn for measurements of baseline data and baseline hemodynamic data were recorded.

Stepwise increase and maintenance of constant propofol plasma concentrations were accomplished with a combination of a bolus injection (over 20 sec) and subsequent exponentially declining infusion rates. A computer-driven syringe pump administered the infusion which began at initial relatively rapid rates and declined asymptotically to the maintenance rates according to the formulas derived by Kruger–Theimer (20) and subsequently applied by Schwilden et al. (21) in the "bolus excretion transfer" scheme. The infusion was maintained for 10 min at which time blood was collected for measurement of plasma concentrations. At 12.5 min after the infusion commenced, hemodynamic data were recorded, and at 15 min another blood sample was collected for measurement of plasma propofol concentration. A revised dose of propofol was then administered by bolus injection and the infusion rate readjusted in order to maintain the new plasma concentration. After another 10 and 15 min, blood was again collected, hemodynamic data was recorded at 12.5 min, and the process was repeated thereafter for a total of nine measurement sets per experiment. This method was chosen to ensure that the hemodynamic data would be representative of a reasonably steady state.

At the end of the infusion study, the propofol administration was stopped and at 15-min intervals, the drug plasma concentration as well as the hemodynamic data were recorded for a further 60 min. Thereafter the animals were killed with a bolus injection of potassium chloride and the position of all the catheters verified by postmortem dissection.

In a separate study, seven pigs were subjected to a similar anesthetic and surgical technique but were left undisturbed for 2.5 hr. Hemodynamic parameters were recorded after completion of the surgery and again 45 min and 2.5 hr later. This study was done to evaluate the effect of time on our model.

Statistical Analysis

Hemodynamic data were analyzed in two sets: (1) data obtained during the phases in which the plasma propofol concentrations were increased and maintained at constant levels; and (2) data obtained from the distribution and elimination phase of propofol after termination of the infusion. The relationship between the plasma concentration of propofol and cardiovascular parameters was evaluated by parametric and nonparametric (MRANK) regression in each animal. When a significant relationship between blood concentration and a cardiovascular variable was obtained, the slope of the simple linear regression model (i.e., the rate of change) was examined further. Analyses of covariance determined whether the slopes for the various animals were similar and an optimal weighted mean slope for a particular variable was calculated (22,23).

The Pearson correlation coefficient was used to estimate the correlation between propofol plasma concentration and the output from the electrochemical detector. Significant differences between the

Table 2. Hemodynamics during the Decrease in Blood Propofol after the Infusion of the Drug was Stopped

Time (min)	Propofol blood concentration (µg/mL)	HR (bpm)	MAP (mm Hg)	Pes (mm Hg)	LVEDP (mm Hg)	SV (mL)	CO (L/min)	L_{max} (mm)	dL (mm)	dL% (%)	dp/dt$_{max}$ (mm Hg/sec)	E_{es} (mm Hg/mm)	L_0 (mm)	E_a (mm Hg/mL)	Ro (mm Hg·sec^{-1}·mL^{-1})	Rp (mm Hg·sec^{-1}·mL^{-1})	C (mL/mm Hg)
0	7.73 ±0.94	110.13 ±3.91	84.34 ±5.21	87.53 ±4.32	13.43 ±0.97	24.10 ±1.17	2.65 ±0.14	11.03 ±0.90	2.02 ±0.25	17.81 ±1.08	−1263.65 ±81.65	43.14 ±9.90	6.61 ±0.78	3.94 ±0.63	0.18 ±0.06	1.82 ±0.32	0.90 ±0.23
15	4.47 ±0.67	112.11 ±3.79	84.86 ±4.59	87.29 ±4.23	11.71 ±1.29	24.90 ±1.13	2.78 ±0.12	10.56 ±0.88	1.87 ±0.25	17.26 ±1.23	−1323.02 ±68.32	56.30 ±13.96	6.19 ±0.68	4.22 ±0.56	0.18 ±0.06	1.72 ±0.18	0.72 ±0.14
30	2.59 ±0.39	115.08 ±4.00	81.78 ±4.03	84.03 ±3.23	12.50 ±0.93	24.24 ±1.36	2.77 ±0.13	10.57 ±0.75	1.90 ±0.26	17.40 ±1.40	−1285.07 ±61.42	51.21 ±14.90	6.14 ±0.45	4.02 ±0.54	0.18 ±0.05	1.68 ±0.18	0.97 ±0.18
45	2.11 ±0.25	101.83 ±3.88	74.80 ±4.50	76.07 ±3.86	13.14 ±1.07	22.14 ±1.32	2.21 ±0.16	12.15 ±0.84	1.80 ±0.29	18.09 ±1.64	−1088.13 ±58.30	50.39 ±12.89	8.76 ±0.56	4.10 ±0.77	0.19 ±0.06	1.56 ±0.21	0.98 ±0.11
60	1.63 ±0.25	114.09 ±4.92	82.33 ±4.83	84.36 ±4.35	12.00 ±1.07	21.87 ±1.29	2.48 ±0.14	10.49 ±0.84	1.76 ±0.26	16.16 ±1.39	−1261.16 ±51.16	41.59 ±9.28	6.15 ±0.59	4.54 ±0.74	0.15 ±0.02	1.94 ±0.18	0.89 ±0.17

Values indicated at time zero are the values obtained at the peak propofol blood concentration during the infusion. Values are $\bar{X}$,SEM for eight animals. Abbreviations and statistical association are discussed in the text.

blood concentrations of propofol at 10 and 15 min were tested with the Wilcoxon signed rank test.

In the control study, the paired t-test (two-tailed) was used to evaluate statistical differences between values obtained at time zero and after 150 min. A P value < 0.05 was accepted as indicating statistical significance.

Results

All results are given as the mean and SEM for eight animals.

1. *Hemodynamic Data*
   (a) *Increasing concentrations of propofol.* Table 1 shows the general hemodynamic data and the plasma propofol concentrations. Statistical analyses were performed on data from each animal separately as plasma concentrations were not similar in the nine steps in all animals. A significant correlation between cardiovascular parameters (effect) and propofol concentrations could be demonstrated for the following:

   There was a statistically significant negative correlation between HR and plasma propofol concentration. SV and CO also decreased significantly as the plasma propofol concentration increased. Peripheral resistance, Rp, increased significantly as the propofol blood concentration increased, but Ro and C did not change. Arterial impedance remained unchanged and regional shortening, normalized for $100/L_{max}$, decreased as the propofol concentration increased. L_{max}, Pes, and MAP remained constant. Myocardial contractility, measured by E_{es}, correlated inversely with plasma propofol concentrations (Figure 2).

   (b) *Propofol plasma concentrations and hemodynamic data after the propofol infusion was terminated.* The relevant data are shown in Table 2. The MRANK test for correlation between the plasma concentration of propofol and cardiovascular effects indicated a statistically significant negative correlation for SV, although this was nonlinear and nonhomogenous. There was also a significant negative correlation of L_{max} and plasma concentration of propofol, a correlation that was linear and homogenous. E_{es} did not return to baseline values as the plasma propofol concentration decreased (Figure 3).

2. *Control Studies* (Table 3)
   HR increased significantly with time from 113.82 ± 8.39 to 126.64 ± 8.47 beats/min. End-systolic

Figure 3. The apparent hysteresis in myocardial contractility as the blood concentration for propofol was increased and decreased. The closed circles are the means for the increasing values and the squares are the mean for the decreasing values, i.e., after the propofol infusion was stopped. The arrowheads indicate the consecutive steps. All values are the mean and SEM for eight experiments.
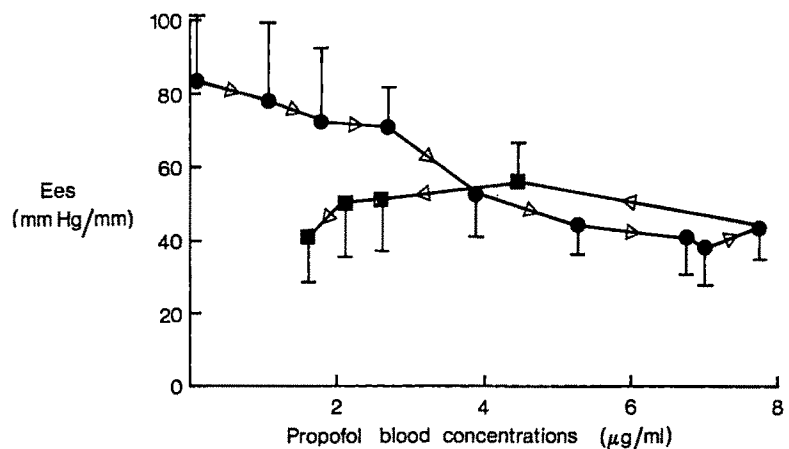
pressure also increased from 83.00 ± 4.02 to 96.73 ± 4.22 mm Hg. Neither myocardial contractility nor effective arterial elastance, E_a, changed with time.

Discussion

This study was designed to compare different plasma levels of propofol, given as a constant infusion, with various hemodynamic parameters. The results indicate a significant inverse correlation between the CO and propofol plasma concentrations due to decreasing HR and SV. SV is directly related to both preload (within certain limits) and myocardial contractility and is inversely related to afterload. The cause for the reduction in SV should be sought in these variables. LV end-diastolic volume, (estimated indirectly from the value of L_{max}, i.e., the regional length at the end of diastole), did not correlate with propofol plasma concentrations, and it is therefore unlikely that changes in diastolic volume could explain the change in the SV. The afterload, characterized by the effective arterial elastance (E_a) in this study, did not increase as propofol plasma concentration increased. However, when we examined the various components of E_a, (i.e., Ro, Rp, and C) separately, Rp correlated positively with propofol plasma concentration. The inverse relationship between SV and afterload is well known (24), and we conclude that in our experimental model, increases in peripheral resistance (Rp) at higher plasma propofol concentrations were partially responsible for the observed decreases in SV.

Myocardial contractility, measured by the end-systolic pressure-length relationship (E_{es}), correlated inversely with the plasma concentrations of propofol. It appears that plasma concentrations in excess of a mean value of 2.69 μg/mL (range 1.58 to 4.8 μg/mL),

with all the values except one in excess of 2.4 μg/mL, were associated with decreases in Ees. It is noteworthy that the decrease in SV and increase in Rp achieved prominence at these plasma concentrations.

We provide evidence that propofol depresses myocardial contractility but fail to explain the observed increase in Rp. Most previous studies indicated a significant reduction in mean arterial pressure and calculated systemic vascular resistance after propofol administration (2–7). We cannot separate the effect of the preexisting anesthetic technique from the effect of propofol and can therefore only speculate as to why our results differ from those previously reported. In order to examine the effect of time on our experimental model, we subjected seven animals to the basic anesthetic technique and surgery without infusing propofol. Only the HR and Pes increased significantly while Rp and E_{es} remained constant.

We reject the possibility that inadequate anesthesia led to increasing Rp during propofol infusion as increasing propofol levels produced progressive depression of the electroencephalogram.

An increase in blood catecholamine levels could explain an increase in Rp, but in our study contractility decreased and HR remained constant, contrasting with the expected changes caused by increasing catecholamine concentrations. One could argue that propofol depressed contractility, and, if there was a catecholamine response, we recorded the balance of the peripheral and central interactions, and the improvement in contractility (due to catecholamines) was obscured by the depressing effect of propofol, while on the peripheral level, the interaction was less pronounced. However, the increase in Rp was only of the order of 15%, and, in addition, total impedance remained unchanged. We are therefore less perturbed by the slight increase in Rp than by the fact that we could not demonstrate a decrease in MAP as

Table 3. The Effect of the Background Anesthetic Technique, Surgery, and Time on Hemodynamic Data of Seven Pigs

Time (min)	HR (bpm)	MAP (mm Hg)	LVEDP (mm Hg)	CO (L/m)	SV (mL)	E_a (mm Hg/mL)	Ro (mm Hg·sec⁻¹·mL⁻¹)	Rp (mm Hg·sec⁻¹·mL⁻¹)	C (mL/mm Hg)	E_{es} (mm Hg/mm)	L_{max} (mm)	dL% (%)	Pes (mm Hg)
0	113.82 ±8.39	78.02 ±4.66	10.22 ±1.20	2.77 ±0.16	25.52 ±2.92	3.92 ±0.42	0.162 ±0.01	1.39 ±0.10	0.94 ±0.09	70.02 ±13.26	12.13 ±0.91	16.78 ±1.80	83.00 ±4.06
150	126.64* ±8.47	82.04 ±6.08	11.10 ±1.02	2.88 ±0.23	23.50 ±1.42	4.22 ±0.60	0.130 ±0.01	1.57 ±0.12	0.80 ±0.05	62.67 ±11.62	12.27 ±0.82	16.27 ±2.15	96.73** ±4.22

Values are X ± SEM. The value at time zero was compared with the value at 150 minutes.
*$P < 0.05$. **$P < 0.005$.

reported by other investigators. Perhaps our method of propofol administration, i.e., starting with a low dose and slowly increasing the plasma concentration, could explain the maintenance of the blood pressure. This aspect requires further study.

Infusion studies were performed by Stephan et al. (4), Monk and colleagues (3), and Vermeyen et al. (25). They found decreases in MAP, CO, and systemic vascular assistance (SVR), while LV filling pressure remained fairly constant. Only in the study of Stephan et al. (4) did SVR remain unchanged (because of equal reductions in MAP and CO). These results, as well as data from studies in which propofol was injected as an intravenous bolus (2,6,7), can be interpreted as indirect evidence that propofol depresses myocardial contractility, based on the observation that SV decreased, even though MAP decreased and preload and HR remained constant. This deduction is based on the principle that SV should increase if the afterload decreases, provided all other parameters remain unchanged. However, this extrapolation assumes that the individual heart rates remained constant, that LVEDP is an acceptable index of LV preload (given the nonlinear relationship of LVEDP to LV end-diastolic volume), and that MAP is an acceptable index of LV afterload. Furthermore, the inherent hazards associated with the unconditional extrapolation from animal experiments to human pathophysiology must be borne in mind. Only one of the studies mentioned, that of Vermeyen, et al. (25), suggests that propofol may cause myocardial depression.

After stopping the propofol infusion, recovery of myocardial contractility was delayed. Our results thus suggest that once myocardial depression has occurred after a prolonged infusion of propofol (and high plasma concentrations), myocardial recovery may not parallel the decrease in the propofol blood levels. The MAP and HR did not correlate with the propofol plasma concentrations while the SV decreased and the L_{max} increased as the propofol concentration decreased. LV afterload was higher at the end of the 60-min wash-out period than at the initial (zero propofol) phase of the study, and the combination of prolonged myocardial depression and an increase in LV afterload (possibly caused by the decreasing levels of anesthesia), explains the decrease in SV and the increase in L_{max} towards the end of the study. However, this hysteresis might not have occurred if the plasma concentrations had not reached the concentrations deliberately employed in this study. Plasma concentrations of propofol decreased by approximately 80% during 1 hr and the EEG changed accordingly to patterns indicating light

anesthesia. It is therefore unlikely that the hysteresis could be explained by high tissue propofol concentrations in the myocardium, as this apparently does not occur in the brain. Again, further studies will have to be conducted to explain this observation, and studies on propofol tissue concentrations are required to clarify this point.

We believe we have demonstrated a dose-related myocardial depression caused by propofol. The generally recommended dose of propofol in patients, viz. 2.0-2.5 mg/kg, certainly produces blood levels that are, for short periods, greatly in excess of those found to cause myocardial depression in the pig. Previous clinical studies do not indicate any serious consequences in healthy patients, but bolus doses of this magnitude in patients with poor myocardial systolic reserve are probably unwise. In these cases smaller intermittent doses should be preferred for induction of anesthesia. Infusion schemes should be based on available pharmacokinetic data, employing loading by infusion (26) or applying the bolus excretion transfer scheme (21), while attempting to avoid exceeding blood levels that affect patient hemodynamic function adversely. One of the limitations in presently available pharmacokinetic data is that they have been obtained from healthy (ASA physical status I and II) patients (27). It is likely that cardiovascularly compromised patients will have smaller central volumes of distribution and lower clearances. Dosage schemes based on pharmacokinetic data obtained from healthy patients may lead to higher than anticipated blood levels. These problems are currently under investigation in our department.

APPENDIX A. Data Related to the Pharmacokinetics and Propofol Determination Applied in this Study.

1. *Results pertaining to the method employed for propofol measurements:*
   Figure A1 demonstrates the linear standard curves (R = 0.99) obtained for propofol dissolved in drug-free serum for 4 consecutive days of use of the apparatus. The detector was polished after 4 days of use so that sensitivity could be restored to that of day 1.
2. *Elution profile of propofol:*
   An example of the elution profile is shown in Figure A2.
3. *Pharmacokinetic data obtained from three animals:*
   Table A1 and Figure A3 show pharmacokinetic data for propofol in three pigs. These data were applied in the subsequent study on the eight animals.
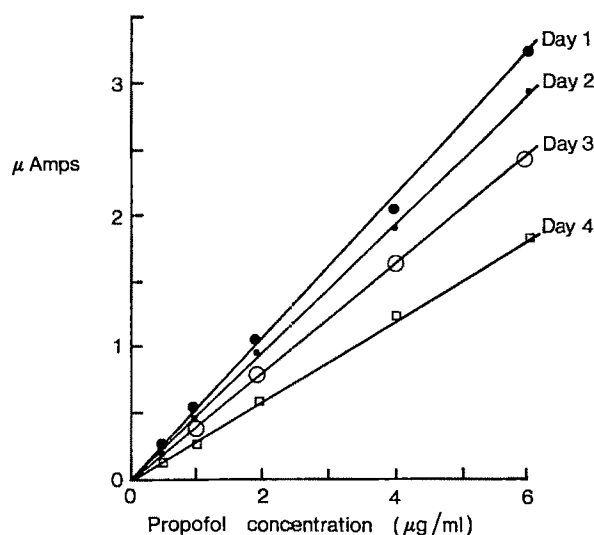
Figure A1. Standard curves for the determination of propofol concentration obtained during 4 consecutive days of analyzing 30 samples per day.
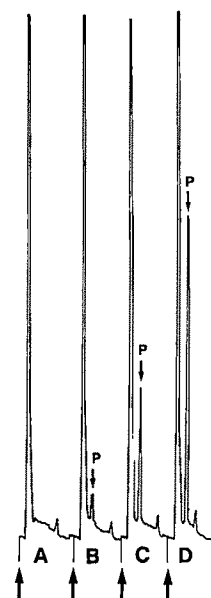
Figure A2. Elution profiles of propofol in drug free serum. Chromatogram A was drug free serum alone while B, C, and D contained 0.4, 2.0, and 4.0 µg/nL propofol respectively.

P denotes the propofol peak which eluded 2.5 min after injection of the sample. The time between injection of the different samples was approximately 5 min as indicated by the arrows below the chromatograph.

4. *Steady state plasma concentrations of propofol:*
   The aim of the dosage scheme was to provide incrementing plateau plasma levels during the period the cardiovascular variables were recorded. An indication of the degree to which the 10-min (C_{10}) and 15-min (C_{15}) serum concentrations differed is given by the proportion of their difference (dC) to the average of the two concentrations expressed as a percentage.

Table A1. Pharmacokinetic Parameters Obtained after
Bolus Injection of Propofol (2.5 mg/kg) into Three Pigs

	Pig 1	Pig 2	Pig 3	Mean
Mass (kg)	36	38	32	35.3
Dose (mg)	90	95	80	88.3
A (g/mL)	1.8576	4.9974	1.8370	2.8973
B (g/mL)	0.8385	0.9853	0.6680	0.8306
alpha (/min)	0.09944	0.34833	0.16159	0.20312
beta (/min)	0.00780	0.01971	0.00820	0.01190
k10 (/min)	0.02135	0.09299	0.02698	0.04710
k12 (/min)	0.04958	0.20123	0.09371	0.11484
k21 (/min)	0.03630	0.07383	0.04911	0.05031
V1 (L)	29.67	15.88	35.93	27.2
V2 (L)	40.52	43.28	68.56	50.8
Vdss (1)	70.19	59.16	104.49	77.9
Clearance (mL/min)	1169.9	1476.5	969.4	1205.3
t1/2-alpha (min)	6.97	1.99	4.29	4.42
t1/2-beta (min)	88.84	35.16	84.53	69.51

% Difference in propofol concentrations
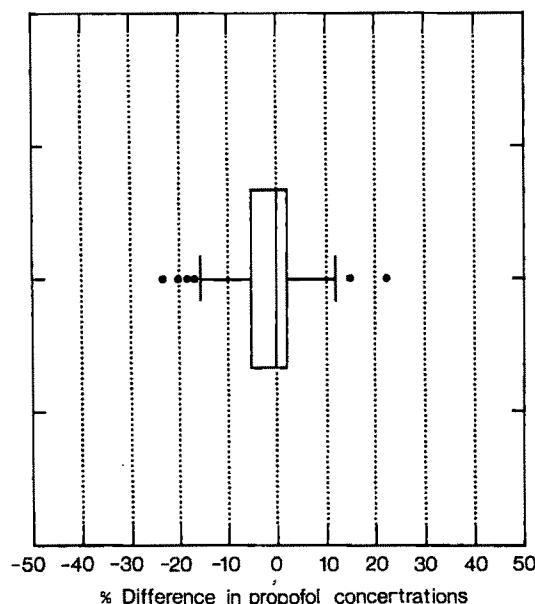
Figure A4. A box-and-whisker plot summarising the difference between the blood concentrations at 10 min and 15 min for propofol (n = the difference between 72 pairs). The median is zero, and the outer solid horizontal lines of the box are the lower and upper quartiles. The whiskers indicate the range and the dots are outlying values. Note that the statistics were performed on the difference between the blood samples at 10 min and 15 min.

Serum propofol concentration (μg/ml)

Time (minutes)
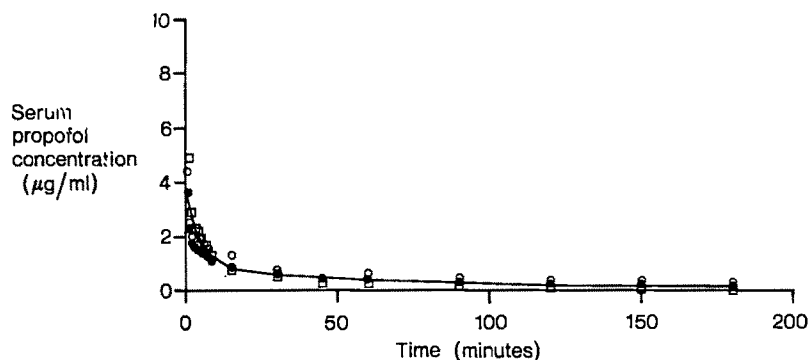
Figure A3. The pharmacokinetic profile of a bolus dose of propofol (2.5 mg/kg) given intravenously to three pigs. The individual curves are indicated with O, ●, and □, while the line represents the fitted mean curve.

$$(dC.200)/(C_{10} - C_{15}) \qquad (3)$$

The mean percentage difference was 1.44% (SEM 1.09%) with the 95% confidence interval −3.64% to 0.75%. The medium percentage difference was 0% with the lower and upper quartiles = 5.22% and 1.87% as illustrated in the box-and-whisker plot in Figure A4.

There was no correlation between the average concentrations obtained, $(C_{10}-C_{15})/2$, and the percentage difference ($R^2 = 0.001$).

No statistically significant difference could be demonstrated between the concentrations at 10 and 15 min for the total of 72 steps ($P = 0.2932$).

The difference between predicted and achieved blood concentration was of little importance as our aim was to demonstrate a possible correlation (or

absence of) between a particular blood concentration of propofol and its effect on the cardiovascular system.

References

1. Adam HK, Briggs LP, Douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35868 in man. Br J Anaesth 1983; 55:97–111.

2. Aun C, Major E. The cardiorespiratory effects of ICI 35868 in patients with valvular heart disease. Anesthesia 1984;39:1096–100.

3. Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to N₂O anaesthesia. Br J Anaesth 1987;59:954–60.

4. Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. Br J Anaesth 1986;58:969–75.

5. Al-Khudhari, Gordon G, Morgan M, Whitwan JG. Acute cardiovascular changes following disoprofol. Anaesthesia 1982;37:1007–10.

6. Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during N_2O anesthesia in humans. Anesth Analg 1987;66:64–70.

7. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. Postgraduate Med J 1986;61(Suppl. 3):23–27.

8. Bugge-Asperheim B, Lernand S, Kiil F. Local dimensional changes of the myocardium measured by ultrasonic technique. Scand J Clin Lab Invest 1969;24:361–71.

9. Sagawa K. The end-systolic pressure-volume relation of the left ventricle. Definition, modification and clinical use. Circulation 1981;63:1223–27.

10. Kaseda S, Tomoike H, Ogata I, Nakamura M. End-systolic pressure-length relations during changes in regional contractile state. Am J Physiol 1984;247:H768–H774.

11. Kaseda S, Tomoike H, Ogata I, Nakamura M. End-systolic pressure-volume, pressure-length and stress-strain relations in the canine heart. J Appl Physiol 1984;294:H648–H654.

12. O'Rourke MF, Taylor MG. Input impedance of the systemic circulation. Circ Res 1967;20:365–85.

13. Westerhof N, Elzinga G, Sipkema P. An artificial arterial system for pumping hearts. J Appl Physiol 1971;31:776–81.

14. Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586–95.

15. Nielsen-Kudsk F. A microcomputer program in BASIC for iterative non-linear data-fitting to pharmacokinetic functions. Int J Biomed Comput 1983;14:95–107.

16. Akaike H. A new look at the statistical model identification. IEEE Trans Aut Control 1973;19:716–23.

17. Wagner JC. Fundamentals of Clinical Pharmacokinetics. 2nd ed. Hamilton, Illinois: Drug Intelligence Publication, 1975.

18. Gibaldi M, Perrier D. Pharmacokinetics. New York: Marcel Dekker, 1975.

19. Schwilden H, Stoeckel H, Schuttler J, Lauven MP. Interactive drug rate control in open loop systems. In H Stoeckel, ed, Quantitation Modelling and Control in Anaesthesia. New York: Springer Verlag, 1975.

20. Kruger-Theimer J. Continuous intravenous infusion and multicompartmental accumulation. Eur J Pharmacol 1968;4:317–24.

21. Schwilden H, Schuttler J, Stoeckel H. Pharmacokinetics are applied to total intravenous anesthesia. Anaesthesia 1983;38:51–52.

22. Hui SL, Berger JO. Emperic Bayes estimation of rates in longitudinal studies. J Am Stat Assoc 1983;78:753–60.

23. Palta M, Cook T. Some considerations in the analyses of rates of change in longitudinal studies. Stat Med 1987;6:599–611.

24. Weber KT, Janicki JS, Hunter WC, Shroff S, Pearlman ES, Fishman AP. The contractile behaviour of the heart and its functional coupling to the circulation. Prog Cardiovasc Dis 1982;14:375–400.

25. Vermeyen KM, Erpels FA, Janssen LA, Buckman CP, Hamegreefs GH. Propofol-fentanyl anesthesia for coronary bypass surgery in patients with good left ventricular function. Br J Anaesth 1987;59:1115–20.

26. Wagner JG. A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Ther 1974;16:691–700.

27. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth Analg 1987;66:1256–63.

Assessment of Spontaneous Ventilation in Anesthetized Children with Use of a Pediatric Circle or a Jackson-Rees System

James P. Conterato, MD, Sten G. E. Lindahl, MD, PhD, Donna M. Meyer, and Jill A. Bires, MD

CONTERATO JP, LINDAHL SGE, MEYER DM, BIRES JA. Assessment of spontaneous ventilation in anesthetized children with use of a pediatric circle or a Jackson-Rees system. Anesth Analg 1989;69:484–90.

To compare respiratory workloads, inspiratory efforts were evaluated in 11 children anesthetized with halothane while breathing through a pediatric circle or a Jackson-Rees system. All underwent urogenital surgery and received caudal analgesia after tracheal intubation. Anesthesia was maintained with O_2/air at an end-tidal halothane concentration of 0.8%. A pediatric circle system at a fresh gas flow (FGF) of 0.5 and 1.5 × min ventilation ($\dot{V}E$) ($C_{0.5}$ and $C_{1.5}$, respectively) and a Jackson-Rees system at FGF of 1.5 and 3.0 × $\dot{V}E$ ($JR_{1.5}$ and $JR_{3.0}$, respectively) were used in each patient in a random order. Tidal volume (VT), mean inspiratory flow (VT divided by the duration of inspiration TI, VT/TI), and the initial fast slopes of the airway occlusion pressure phase ($\Delta P^0/\Delta tFAST$) were significantly lower ($P < 0.05$) with the Jackson-Rees than with the circle system, indicating greater impedence to spontaneous breathing with the Jackson-Rees system. The Jackson-Rees system also required a greater peak transpulmonary pressure ($P_{tp}MAX_e$) than did the circle system to achieve the same peak expiratory flows (V_{MAX_e}, $P < 0.05$), again suggesting an increased resistance with the Jackson-Rees system. These results are most likely explained by the difference in elastic loads (two to three times more with the Jackson-Rees systems) between the two systems. The pediatric circle system appears to be a reliable alternative to the Jackson-Rees system.

Key Words: ANESTHESIA, PEDIATRIC. EQUIPMENT, ANESTHESIA CIRCUITS—Jackson-Rees, circle. ANESTHETIC TECHNIQUES, CIRCLE AND SEMI-OPEN CIRCUITS.

Since the introduction of Ayre's T-piece (1), the pattern of spontaneous respiration and the prevention of rebreathing in semi-open pediatric anesthesia circuits have been studied (2–5). To eliminate rebreathing, high fresh gas flow (FGF) of up to 3 to 3.5 × min ventilation ($\dot{V}E$) are required (6). It was, however, recently shown that FGF settings of 1.5 to 2 × $\dot{V}E$ are satisfactory for elimination of significant rebreathing in spontaneously breathing infants and children during halothane anesthesia (5). These FGFs, however, exceed those commonly used in circle systems. Low flows decrease the consumption of expensive volatile anesthetic agents and improve humidification.

The major concern with circle systems in spontaneously breathing pediatric patients has been the potential for increased resistance across valves and the CO_2 absorption canister. The result of this increase would be a higher respiratory work load that may eventually lead to fatigue (7,8). Kay et al. (9) stated in 1983 that all anesthesia systems (circle, partial rebreathing, as well as nonrebreathing circuits) increased inspiratory and expiratory work. Expiratory work was always increased more than inspiratory work and was proportional to the FGF rate. Recently, Rasch et al. (10) compared a pediatric circle system with a Jackson-Rees pediatric (Mapleson F) system. They found that the systems were essentially equivalent, demonstrating small resistances compared with those measured over endotracheal tubes, particularly when internal diameters were <4.5 mm. They did not, however, investigate ventilation volumes and respiratory efforts.

The objective of our study was to determine whether the choice of a circle or Jackson-Rees circuit and whether the use of different FGFs with each of these circuits has any effect on respiratory work in spontaneously breathing children anesthetized with

Table 1. Patient Data and the Sequence in Which Circuits and Fresh Gas Flows (FGF) Were Used

Patient No.	Body Weight (kg)	Diagnosis	Operation	Circuit and FGF
1	15.1	Hypospadias	Repair	$JR_{3.0}$, $JR_{1.5}$, $C_{1.5}$, $C_{0.5}$
2	11.0	Hypospadias	Repair	$JR_{3.0}$, $JR_{1.5}$, $C_{1.5}$, $C_{0.5}$
3	10.0	Hypospadias	Repair	$JR_{3.0}$, $JR_{1.5}$, $C_{1.5}$, $C_{0.5}$
4	15.2	Hypospadias	Repair	$C_{0.5}$, $C_{1.5}$, $JR_{1.5}$, $JR_{3.0}$
5	10.2	Hypospadias	Repair	$C_{0.5}$, $C_{1.5}$, $JR_{1.5}$, $JR_{3.0}$
6	17.3	Urethral fistula	Closure	$C_{1.5}$, $C_{0.5}$, $JR_{3.0}$, $JR_{1.5}$
7	10.5	Hypospadias	Repair	$C_{0.5}$, $C_{1.5}$, $JR_{1.5}$, $JR_{3.0}$
8	9.5	Epispadias	Repair	$C_{1.5}$, $JR_{1.5}$, $JR_{3.0}$, $C_{0.5}$
9	11.0	Hypospadias	Repair	$JR_{3.0}$, $JR_{1.5}$, $C_{1.5}$, $C_{0.5}$
10	9.6	Hypospadias	Repair	$C_{1.5}$, $C_{0.5}$, $JR_{3.0}$, $JR_{1.5}$
11	11.0	Hypospadias	Repair	$C_{0.5}$, $C_{1.5}$, $JR_{1.5}$, $JR_{3.0}$

$C_{0.5}$ = circle system at a FGF of 0.5 × minute ventilation ($\dot{V}E$); $C_{1.5}$ = circle system at a FGF of 1.5 × minute ventilation ($\dot{V}E$); $JR_{1.5}$ = Jackson-Rees system at a FGF of 1.5 × minute ventilation ($\dot{V}E$); $JR_{3.0}$ = Jackson-Rees system at a FGF of 3.0 × minute ventilation ($\dot{V}E$).

halothane. To assess respiratory work, we examined the impact of system choice and FGF rate on ventilation pattern, respiratory drive and timing, and pulmonary mechanics. The measurements were done in random order, during the same procedure, and on the same child.

Patients and Methods

After approval from the Institutional Review Board at the Mayo Clinic and written parental consent, 11 children (aged 13 months to 3 years; body weight 9.5 to 17.3 kg) were investigated. They were all to undergo urogenital surgery and had no symptoms of cardiorespiratory disease (ASA physical status I). Further patient data are given in Table 1.

Anesthesia

Premedication was not used in any patient. Anesthesia was induced with halothane in O_2/N_2O (F_iO_2 ~ 0.5). The trachea was intubated without the use of muscle relaxants. To obtain an airtight connection (with an airway pressure of at least up to 15 cm H_2O), cuffed tracheal tubes (Mallinckrodt) with internal diameters of 3.5–4.5 mm were used. Caudal anesthesia was established with 0.25% bupivacaine (0.5 mL/kg of body weight) and the patient was allowed to resume spontaneous breathing. General anesthesia was maintained with O_2/air and end-tidal halothane concentrations (ET_{hal}) of at least 0.8 to 0.9% (as measured by mass spectrometry) and administered via either a circle system with pediatric tubing (inner
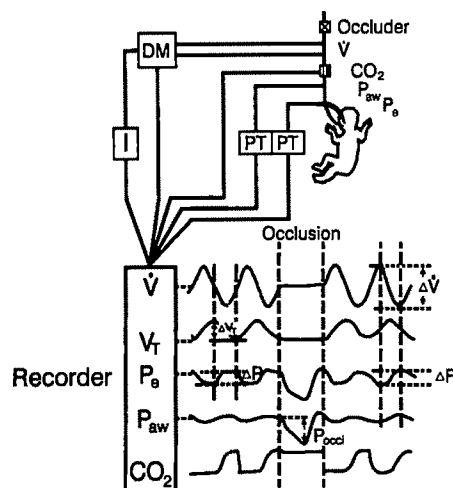
Figure 1. Apparatus used. P_e indicates esophageal pressure and P_{aw} shows position where airway pressures were measured. CO_2 and $\dot{V}$ denote arrangements of in-line CO_2 meter and pneumotachograph. Positioning of occluder is also shown. Typical tracings are shown and one occlusion breath is given. Points for calculation of dynamic compliance (C_{dyn}) and total pulmonary resistance (TPR) are indicated. DM = differential manometer; I = integrator; PT = pressure transducer; V_T = tidal volume.

diameter 16 mm) and adult canisters (Ohio Medical Apparatus, Madison, WI) or a Jackson-Rees system (open-ended bag in the end of the expiratory limb) with the same pediatric tubing as in the circle system. The FGF setting was also varied for the circle system using 0.5 and 1.5 × $\dot{V}E$ and for the Jackson-Rees system using 1.5 and 3.0 × $\dot{V}E$. Airway pressures were atmospheric at the end of expiration with both circuits. The different systems and FGF settings were used in a random order (Table 1). Precordial stethoscope, blood pressure, heart rate, oxygen saturation, axillary temperature, and intermittent gas analyses by mass spectrometry were used for patient monitoring.

Measuring Apparatus

Distal to the Y-piece of the anesthesia circuit, a monitoring module consisting of an airway occluder, an in-line infrared capnometer (Hewlett-Packard, 14360A), and a pneumotachograph (Fleisch no. 0) were placed in the apparatus dead space (Figure 1). This space was 10 mL measured by water displacement. Inspiratory and expiratory resistance of the measuring apparatus were 14 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$ at a flow rate of 6 L/min. The inspiratory resistances of the circle and Jackson-Rees systems used were similar (Figure 2). Expiratory resistances were similarly low in both systems. The inspiratory and expiratory elastances (measured by different volumes produced
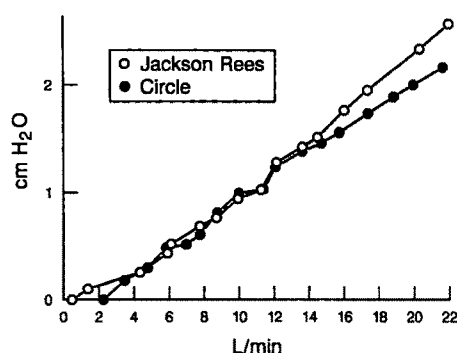
Figure 2. Pressure-flow relations in the pediatric circle (closed dots) and the Jackson-Rees system (open dots).

by a supersyringe and their resulting pressures) of the pediatric circle system were 0.19 and 0.13 cm H_2O/mL, respectively. Corresponding values for the Jackson-Rees system were 0.57 and 0.30 cm H_2O/mL.

$\dot{V}E$ was measured by electrical integration of the flow signal from the heated pneumotachograph and a differential manometer (Microswitch, Honeywell, 170 PC). The capnometer, which was a nonsampling monitor and thus unaffected by high FGF, was positioned between the pneumotachograph and the occluder, had a response time of 190 msec, and achieved a well identified end-tidal plateau in all patients. The in-line capnometer also served to indicate the level of rebreathing and to detect any leakage in the system during occlusion tests. Airway pressures were measured between the pneumotachograph and the tracheal tube connector (Microswitch, Honeywell, 170 PC). This point was also used for intermittent sampling of respiratory gases to the mass spectrometer. Esophageal pressures, from an estimated position in the lower third of the esophagus, were measured (Microswitch, Honeywell, 170 PC) by air-filled balloon-tipped catheters. To accept transpulmonary pressures for the calculation of dynamic compliance (C_{dyn}) and total pulmonary resistance (TPR), a ratio of 0.9 to 1.1 between esophageal and airway occlusion pressures was required. This ratio was achieved in 7 of 11 patients.

Recordings and Calculations

Signals for flow, volume, CO_2, airway, esophageal, and transpulmonary pressures were recorded on a six-channel recorder (General Scanning, RS6-5P). $\dot{V}E$ was calculated as the product of tidal volume (V_T) and respiratory rate (f) during 30-sec intervals. Duration of inspiration (T_I) and duration of the whole respiratory cycle (T_{TOT}) were measured from flow tracings, and the ratio of the two (T_I/T_{TOT}) was

calculated. The mean inspiratory flow (V_T/T_I, mL/sec) was also calculated. The airway occluder (response time 0.03 sec) was electrically controlled by the pneumotachograph so that occlusion occurred precisely when expiration switched to inspiration; that is, at the actual functional residual capacity (FRC). Occlusion tests were done for two consecutive breaths. The first breath was used for detailed analysis. Occlusion pressures after 0.1 sec ($P°0.1$) as well as the maximal occlusion pressures ($P°MAX$) were measured. The occlusion pressure curve was biphasic in all patients in agreement with earlier observations (11), with an initial fast phase and a later slower phase (Figure 1). The pressure drop during 0.1 sec of the fast as well as of the slow phase ($\Delta P°/\Delta t_{FAST}$, $\Delta F°/\Delta t_{SLOW}$, respectively) were measured. C_{dyn} and TPR were calculated according to the following formulas.

$$C_{dyn} \text{ (mL/cm } H_2O) = \frac{\Delta \bar{V}_T}{P_E - P_I}$$

$$TPR \text{ (cm } H_2O \cdot L^{-1} \cdot sec^{-1}) = \frac{P_E - P_I}{\Delta \dot{V}}.$$

P_I and P_E are the mean of seven transpulmonary pressures calculated during zero flow after inspiration (P_I) and expiration (P_E) for calculations of C_{dyn} and at midvolume points during inspiration and expiration for calculations of TPR (see Figure 1).

Calibrations

Flow and volume were calibrated with an accurate pump at flows of 50 and 100 mL/sec, delivering a volume of 100 mL. The flow from the pump was checked against a precision rotameter and the volume with a spirometer. The reproducibility of the pump was within ±0.25%; repeated measurements were made. Flow and volume calibrations, done before each measurement, were performed with the same gas composition, temperature and humidification that were used during the actual measurements. Transducers for airway and esophageal pressure measurements were calibrated before and after measurements against a 30-cm column of water. The capnometer was calibrated before each measurement with analyzed gas mixtures that had CO_2 concentrations between 1 and 7.5% (gas mixtures prepared gravimetrically after actual weight and percentage was determined by gas chromatography). There was no time lag between different channels on the recorder. The mass spectrometer was routinely calibrated for clinical use and before each measurement by certified gases.

Table 2. Mean Values ($\pm$SD) of Mean Arterial Blood Pressure (MAP), Heart Rate (HR), Oxygen Saturation (SaO$_2$), and End-tidal Halothane Concentrations (ET$_{hal}$) for the Different Systems and Fresh Gas Flow Settings

	MAP (mm Hg)	HR (beats/min)	SaO$_2$ (%)	ET$_{hal}$ (%)	IMAXCO$_2$ (%)
C$_{0.5}$	63 $\pm$ 18	123 $\pm$ 11	99 $\pm$ 1	0.8 $\pm$ 0.3	0
C$_{1.5}$	64 $\pm$ 17	122 $\pm$ 12	99 $\pm$ 1	0.8 $\pm$ 0.2	0
JR$_{1.5}$	62 $\pm$ 16	121 $\pm$ 11	99 $\pm$ 1	0.8 $\pm$ 0.2	0.3 $\pm$ 0.3
JR$_{3.0}$	65 $\pm$ 15	121 $\pm$ 12	99 $\pm$ 1	0.8 $\pm$ 0.2	0

Procedure

The anesthetic management was standardized as far as possible, and no measurements were done until 30 min after induction of anesthesia and after the start of surgery, when the caudal anesthesia had proved to be effective for the surgical procedure. $\dot{V}$E measured 15 to 20 min after administering the caudal anesthetic (with the initial settings on the pediatric circle system in use) was then used for the calculation of FGF settings throughout the study. The following settings were investigated. Pediatric circle system: FGF 0.5 $\times$ $\dot{V}$E (C$_{0.5}$) and FGF 1.5 $\times$ $\dot{V}$E (C$_{1.5}$). Jackson-Rees system: FGF 1.5 $\times$ $\dot{V}$E (JR$_{1.5}$) and FGF 3.0 $\times$ $\dot{V}$E (JR$_{3.0}$).

Alterations between different FGF and systems were measured during a 5-min period with repeated measurements every minute and with a final measurement done during the 5th min after which the occlusion test was done. Data are from measurements during the 5th min unless otherwise stated. Gas analyses were performed before and after each 5-min measurement. No gas sampling was done during measurements.

Statistical Analysis

Mean values and standard deviations were calculated. However, for each variable of interest, the effects of treatment for each subject were ranked, and Friedman's two-way analysis of variance by ranks was used to determine the existence of significant differences between the treatments (C$_{0.5}$, C$_{1.5}$, JR$_{1.5}$, JR$_{3.0}$). Multiple comparisons with use of the estimated ranks were performed to determine which treatment effects differed significantly from which others. The P values of the individual comparisons were adjusted so that an overall significance level of $P \leq 0.05$ was maintained.

Because the effect of fresh gas flow rate was found to be insignificant for every variable, the data values for each subject corresponding to the low and high flow rates for each system were pooled, and paired two-tailed t-tests were used to test for differences between the systems. Normality in each group was

checked via Shapiro-Wilks test. A significance level of $P \leq 0.05$ was used for all analyses.

Results

There were no changes in heart rate, blood pressure, or respiratory rate at the start of surgery, indicating an effective caudal block. Mean blood pressure, heart rate, oxygen saturation, and ET$_{hal}$ concentration were unchanged when different circuits and FGF settings were used. The mean maximal inspired CO$_2$ concentration (IMAXCO$_2$) was 0.3 $\pm$ 0.3% at JR$_{1.5}$ (range 0–0.9%) and was negligible at all other settings (Table 2).

Influence of FGF Settings

There was no difference in VT, ETCO$_2$, or any component of the occlusion pressure (P^{o}0.1, P^{o}MAX, ΔP^o/ΔtFAST, ΔP^o/ΔtSLOW) when FGF was increased from 0.5 to 1.5 $\times$ $\dot{V}$E in the circle system or from 1.5 to 3.0 $\times$ $\dot{V}$E in the Jackson-Rees system. This result was also true for maximal inspiratory flows ($\dot{V}$MAX$_i$), maximal expiratory flows ($\dot{V}$MAX$_e$), and corresponding transpulmonary pressures (P$_{tp}$MAX$_i$, P$_{tp}$MAX$_e$). Because of these results, we were able to pool the high and low FGF data from each system and perform paired two-tailed t-tests to test for differences between the systems.

Circle and Jackson-Rees Systems

(1) Tidal Volume and Minute Ventilation. Respiratory rate (f), end-tidal CO$_2$ (ETCO$_2$), and respiratory timing (Tı/TTOT) were similar with both systems (Table 3). However, tidal volume (VT), minute ventilation ($\dot{V}$E), and mean inspiratory flow (VT/Tı) were all significantly greater with the circle system than with the Jackson-Rees system (Table 3).

(2) Occlusion Pressure Analysis. ΔP^o/ΔtFAST was steeper with the circle system than with the Jackson-

Table 3. Mean Values (±SD) of Tidal Volume (VT),
Respiratory Rate (f), Minute Ventilation (VE), End-tidal
CO_2 Concentration (ETco₂), Mean Inspiratory Flow
(VT/TI), and Respiratory Time Ratio Between Duration of
Inspiration (TI) and Duration of the Whole Respiratory
Cycle (TTOT)

Variable	Mean Values (SD)		Significance of Difference (P)
	Circle	Jackson-Rees	
VT (mL/kg)	5.67 (1.03)	5.04 (1.10)	0.003
f (breaths/min)	35.18 (3.82)	34.84 (3.65)	0.665
VE (mL·min⁻¹·kg⁻¹)	196.49 (30.47)	170.85 (32.94)	0.013
ETco₂ (vol %)	6.13 (0.70)	6.04 (0.65)	0.137
VT/TI (mL/sec)	7.72 (1.32)	6.44 (0.98)	0.008
TI/TTOT	0.42 (0.03)	0.44 (0.02)	0.322

Table 4. Mean Values (±SD) for Airway Occlusion
Pressures at 0.1 sec (P°0.1) and Their Maxima (P°MAX)
and for the Initial Fast Slope (ΔP°/ΔtFAST) and Later Slow
Slope (ΔP°/ΔtSLOW) of the Occlusion Pressure Curve

Variable	Mean Values (SD)		Significance of Difference (P)
	Circle	Jackson-Rees	
P°0.1 (cm H₂O)	3.32 (0.83)	2.76 (1.37)	0.227
ΔP°/ΔtFAST (cm H₂O/sec)	40.77 (9.33)	32.32 (4.44)	0.011
P°MAX (cm H₂O)	18.84 (4.97)	17.99 (4.84)	0.201
ΔP°/ΔtSLOW (cm H₂O/sec)	14.06 (6.13)	12.37 (5.67)	0.244

Table 5. Mean Values (±SD) of Dynamic Compliance
(C_{dyn}) and Total Pulmonary Resistance (TPR) With the
Different Circuits*

Variable	Mean Values (SD)		Significance of Difference (P)
	Circle	Jackson-Rees	
C_{dyn} (mL·cm H₂O⁻¹·kg⁻¹)	1.22 (0.46)	1.11 (0.31)	0.229
TPR (cm H₂O·L⁻¹·sec⁻¹)	19.71 (10.44)	23.57 (12.65)	0.125

*Data based on the 7 children with acceptable esophageal pressures.

Table 6. Transpulmonary Pressures (P_{tp}MAX) at Maximal
Flow Rates (VMAX) during Inspiration and Expiration
with the Different Circuits

Variable	Mean Values (SD)		Significance of Difference (P)
	Circle	Jackson-Rees	
P_{tp}MAX(i) cm H₂O	2.39 (4.36)	2.11 (4.87)	0.593
P_{tp}MAX(e) cm H₂O	−1.03 (3.14)	−2.38 (2.71)	0.027
VMAX(i) mL/sec	137.86 (53.43)	124.14 (45.36)	0.006
VMAX(e) mL/sec	123.79 (51.67)	108.64 (34.52)	0.116

(P_{tp}MAX$_e$) achieved for those flows were significantly
less in the circle system (Table 6).

Rees system, suggesting less resistance to inspiration
with the circle system (Table 4). Other components of
the two systems' occlusion pressures (P°0.1, P°MAX,
ΔP°(Δt$_{slow}$)) were not significantly different (Table 4).

(3) *Dynamic Compliance and Total Pulmonary Resis-
tance.* There were no major differences between sys-
tems for dynamic compliance (C_{dyn}) or total pulmo-
nary resistance (TPR) among the seven subjects in
whom we were able to achieve adequate correlation
between the esophageal balloon pressures and air-
way occlusion pressures (Table 5).

(4) *Peak Transpulmonary Pressures and Flows.* Despite
the fact that a greater tidal volume was moved during
inspiration with the circle system, there was no
significant difference between the circle and Jackson-
Rees systems for peak inspiratory transpulmonary
pressure (P_{tp}MAX$_i$), whereas peak inspiratory flow
rate (VMAX$_i$) was significantly greater for the circle
system (Table 6). Conversely, on expiration, the peak
expiratory flow rates (VMAX$_e$) for the circle and Jack-
son-Rees systems were not significantly different
but the peak expiratory transpulmonary pressures

Discussion

The ventilatory responses of the anesthetized child
and adult to resistive loads (7,8), hypoxic stress (12),
and rebreathing (5,6,11,13) have been characterized
in prior studies and are pertinent to the interpretation
of our results.

The ventilatory response typically elicited by a
resistive load in conscious subjects is to prolong the
inspiratory phase, lower peak inspiratory flow rate,
and increase inspiratory drive (increased occlusion
pressure) (14). This response is mediated by neural
reflexes, initiated in the lung, and results in immedi-
ate feedback and interaction between stretch recep-
tors and muscle spindles (14). As shown by Whitelaw
et al. (7), this reflex response is lost and VT decreases
during methoxyflurane anesthesia when respiratory
resistances as high as 40 cm H₂O·L⁻¹·sec⁻¹ are used.
In the present series, VT and VT/TI were lower and
ΔP°/ΔtFAST was decreased with the Jackson-Rees
compared with those the circle system. This result
was most probably due to the difference in elastic
respiratory loads between the two systems.

Lower VT and VT/TI are not only indicative of an
increased respiratory load but they could also have

been caused by a deeper anesthetic level or a variable effect of the caudal anesthesia when the Jackson-Rees system was used. Evidence that this possibility was not the case include the fact that the studies were performed in a random order; the uptake of halothane was in a near steady state before measurements started; ET_{hal} was similar with the circle and the Jackson-Rees systems; and heart rate, blood pressure, and f were unchanged at the start of surgery in all cases, indicating good surgical analgesia from the caudal blocks, which were always evaluated before measurements were done. The dose of bupivicaine used (0.5 mL/kg of 0.25% bupivicaine) could theoretically affect chest wall function during breathing. However, patients served as their own controls, which would nullify this hypothetical effect. There were no signs of hypoxia at any stage during the investigation. Besides, ventilatory response to hypoxic stimulation is nearly eliminated during the levels of halothane anesthesia that were used in this study (12). Hypercarbia and rebreathing were also eliminated as explanatory factors for the greater V_T with the circle system because $ETco_2$ was the same and rebreathing did not occur when the circle system was used. In the Jackson-Rees system, on the other hand, the mean value of $IMaxCO_2$ was 0.3% at a FGF of 1.5 × $\dot{V}E$, which could have acted as a respiratory stimulant. This result was not the case because V_T was smaller with $JR_{1.5}$ than with $C_{1.5}$. In agreement with an earlier study (5), this level of rebreathing is not great enough to result in clinically significant rebreathing, not even in the case that had the highest $IMaxCO_2$ of 0.9%. Because each child acted as its own control and the only changes employed were the anesthetic systems and FGF settings, the most likely explanation for lower V_T and V_T/T_I ratios and a more retarded $\Delta P^o/\Delta t_{FAST}$ with the Jackson-Rees system was a respiratory load higher with this system than with that of the circle system.

Prior studies (8,15,16) that examined the ventilatory response to resistive loads in anesthetized individuals demonstrated a ventilatory compensation over time to restore V_T with increased mechanical resistances. We did not see this kind of response during the 5-min period after a change from the circle circuit to the Jackson-Rees circuit or in going from the Jackson-Rees to the circle circuit. However, in two of the previous studies of resistive breathing (8,15), $ETco_2$ and arterial CO_2 concentrations increased with resistive loading, suggesting that chemical stimulation of breathing may have been the mechanism underlying the ventilatory compensation seen in these prior studies. In the present study, $ETco_2$ stayed the same with both systems as well as with

both fresh gas flows used. The mechanical resistances used in the prior studies where $ETco_2$ increased were greater than those in our study; nonetheless, it is somewhat surprising that $ETco_2$ did not increase when the V_T and $\dot{V}E$ decreased with the Jackson-Rees circuit. It is doubtful that this lack of a change in $ETco_2$ could be explained by an effect of different fresh gas flows on our capnometer's reading because the device used was a nonsampling type that is unaffected by fresh gas flow settings. The respiratory dead space could have been greater with the circle circuit, due to atelectasis for instance, which would result in a falsely low $ETco_2$ reading with the circle circuit and explain the higher V_T and $\dot{V}E$ with the circle system. This possibility is not supported, however, by any change in dynamic compliance with circle system (Table 5). Also, V_T changes were essentially immediate when changing from circle to Jackson-Rees system and vice versa, too fast to be explained by CO_2 retention.

An unchanged $ETco_2$, however, is in agreement with Rasch et al. (10), who found in a comparison between a pediatric circle system and a Jackson-Rees system $ETco_2$ and respiratory rate to be unaltered, although they used the two systems in different patients. This result may also be an indicator of the fact that the inspiratory resistance was virtually the same in the Jackson-Rees and the circle system (Figure 2) and, hence, that there should not be any measurable respiratory difference in children when breathing through one or the other of the two systems studied. Inspiratory mechanical resistance, however, is not the only factor that can increase respiratory load in children or adults who are connected to various anesthetic systems. Moote et al. (15) demonstrated that variations in elastic loads of anesthetic circuits result in the same ventilatory response as if mechanical resistances were altered. When a circle system with a large gas volume and, hence, a low elastic load is changed into one with a small gas volume (like a Jackson-Rees system), the elastic load is increased. In the present study, the inspiratory as well as the expiratory elastances of the Jackson-Rees system were almost three times greater than those in the pediatric circle system. It appears that the difference in elastic loads between the two systems is the explanation for the impact on breathing that the change in circuits had on the children in this study. This explanation is also supported by the fact that the circle system achieved a significantly higher peak inspiratory flow rate than that of the Jackson-Rees system with no difference in peak transpulmonary inspiratory pressure. Similarly, the circle system required a significantly lower peak transpulmonary

expiratory pressure to attain the same peak expiratory flow rate as that of the Jackson-Rees system. Kay et al. (9) reached similar conclusions that flow-dependent resistance is more pronounced during expiration in semi-open anesthetic systems than that in circle systems.

In summary, we found that there were ventilatory differences between circle and Jackson-Rees systems when used for spontaneous breathing during general anesthesia. The Jackson-Rees system resulted in decreased V_T and V_T/T_I and decrease the initial fast phase of occlusion pressures compared with the circle system. This occurrence was most probably due to differences in elastic resistance between the two systems. Whether the additional load imposed by the Jackson-Rees system is of clinical significance or not should be addressed in a study of spontaneous breathing via circle and Jackson-Rees systems with regard to development of fatigue. Certainly, for surgical procedures in which spontaneous breathing is deemed appropriate, the circle system appears to be a good and reliable alternative.

References

1. Ayre P. Anaesthesia for hare-lip and cleft palate operations on babies. Br J Surg 1937;25:131-2.

2. Kain ML, Nunn JF. Fresh gas economics of the Magill circuit. Anesthesiology 1968;29:964-74.

3. Willis BA, Pender JW, Mapleson WW. Rebreathing in a T-piece: volunteer and theoretical studies of the Jackson-Rees modification of Ayre's T-piece during spontaneous respiration. Br J Anaesth 1975;47:1239-45.

4. Meakin G, Coates AL. An evaluation of rebreathing with the Bain system during anaesthesia with spontaneous ventilation. Br J Anaesth 1983;55:487-95.

5. Lindahl SGE, Charlton AJ, Hatch DJ. Ventilatory responses to rebreathing and carbon dioxide inhalation during anaesthesia in children. Br J Anaesth 1985;57:1188-96.

6. Lindahl SGE, Charlton AJ, Hatch DJ. Accuracy of prediction of fresh gas flow requirements during spontaneous breathing with the T-piece. Eur J Anaesthesiol 1984;1:269-74.

7. Whitelaw WA, Derenne J-P, Couture J. Milic-Emili J. Adaptation of anesthetized men to breathing through an inspiratory resistor. J Appl Physiol 1976;41:285-91.

8. Lindahl SGE, Charlton AJ, Hatch DJ, Phythyon JM. Ventilatory responses to inspiratory mechanical loads in spontaneously breathing children during halothane anaesthesia. Acta Anaesthesiol Scand 1986;30:122-7.

9. Kay B, Beatty CW, Healy TEJ, Accush MEA, Calpin M. Change in the work of breathing imposed by five anaesthetic breathing systems. Br J Anaesth 1983;55:1239-46.

10. Rasch DK, Bunegin L, Ledbetter J, Kaminskas D. Comparison of circle absorber and Jackson-Rees systems for paediatric anaesthesia. Can J Anaesth 1988;35:25-30.

11. Lindahl SGE, Olsson A-K. Respiratory drive and timing before and during CO_2 inhalation in infants anaesthetized with halothane. Eur J Anaesthesiol 1986;3:427-37.

12. Knill RL, Gelb AW. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiology 1978;49:244-51.

13. Byrick RJ. Respiratory compensation during spontaneous ventilation with the Bain circuit. Can Anaesth Soc J 1980;27:96-105.

14. Jordan C. Assessment of the effects of drugs on respiration. Br J Anaesth 1982;54:763-82.

15. Moote CA, Knill RL, Clement J. Ventilatory compensation for continuous inspiratory resistive and elastic loads during halothane anesthesia in humans. Anesthesiology 1986;64:582-9.

16. Zin WA, Behrakis PK, Luijendijk SCM, Higgs AB, Böddener A, Milic-Emili J. Immediate response to resistive loading in anesthetized humans. J Appl Physiol 1986;60:506-12.

Comparative Effects of Halothane and Isoflurane Anesthesia on the Ultrastructure of Human Hepatic Cells

Gérard Goldfarb, MD, Edith Rogier, PhD, Christophe Gebauer, MD, Claudine Lassen, MD, Dominique Bernuau, MD, Pierre Jolis, MD, and Gérard Feldmann, MD

GOLDFARB G, ROGIER E, GEBAUER C, LASSEN C, BERNUAU D, JOLIS P, FELDMANN G. Comparative effects of halothane and isoflurane anesthesia on the ultrastructure of human hepatic cells. Anesth Analg 1989;69:491-5.

The effects of halothane and isoflurane on the ultrastructure of the liver cells in adult patients with normal liver-function tests were compared. After induction of anesthesia with thiopental, fentanyl, and pancuronium, 18 patients were randomly divided into three groups of six each. Anesthesia was maintained with droperidol (droperidol group), with halothane (1.7 MAC, halothane group), or with isoflurane (1.7 MAC, isoflurane group). During the surgical procedure, 1 hr after the induction, a liver biopsy was performed in each patient and processed for light and electron micros-

copy. All biopsies were normal on light microscopy. On electron microscopy, no mitochondrial abnormalities were found. In all three groups, irregular nuclear membranes, dilation of the rough endoplasmic reticulum, and vesiculation of the smooth endoplasmic reticulum were seen, without any significant differences between the groups. There were significantly more lysosomes in the hepatocytes of patients receiving halothane than in the hepatocytes of patients receiving isoflurane or droperidol. This study shows that halothane can induce ultrastructure abnormalities very early after the beginning of its administration while, under the same conditions, isoflurane does not.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. ANESTHETICS, INTRAVENOUS—thiopental. LIVER—hepatotoxicity, halothane, isoflurane.

Although the mechanisms of hepatotoxicity of halogenated anesthetics remain unclear (1), it is commonly thought that a direct toxic effect of these agents or of their metabolites, and a decrease in hepatic oxygen availability are involved (2). In animals, halothane decreases hepatic blood flow (3) and produces, via the reductive pathway, metabolites that can irreversibly bind to hepatic cellular constituents (4–7) and modify the endoplasmic reticulum (8). In contrast with halothane, isoflurane is only slightly metabolized (9) and has little effect on the liver in experimental animals (3,7,10,11). In humans, the incidence of clinical manifestations of halothane hepatitis is low (1/35000) (1), but ultrastructural changes suggesting a cellular response to an acute event are

observed in hepatic cells of patients receiving halothane (12). The purpose of the present study is to compare the respective prevalences of hepatic ultrastructural abnormalities in patients while anesthetized with halothane or isoflurane.

Methods

Eighteen patients (ASA physical status I–II), ranging from 20 to 65 years of age (50 ± 5, mean ± SE), were included in the study after eliciting informed consent and institutional approval. They were scheduled for elective cholecystectomy or gastrectomy. Patients who had undergone general anesthesia in the previous 3 months, patients with a preexisting liver disease or a history of exposure to hepatotoxic drugs, and patients with abnormal liver function tests were excluded. The patients were premedicated 1 hr before induction of anesthesia with hydroxyzine hydrochloride, 100 mg and atropine sulfate, 0.5 mg, intramuscularly. Anesthesia was induced with thiopental (7

mg/kg) and fentanyl (3 μg/kg) followed by pancuronium (0.1 mg/kg) to facilitate tracheal intubation. The patients were mechanically ventilated with a mixture of nitrous oxide, 65% in oxygen. They were randomly allocated to one of the three following groups: in the first group (droperidol group, $n = 6$), anesthesia was maintained with increments of droperidol, fentanyl and pancuronium; in the second group (halothane group, $n = 6$), anesthesia was maintained with halothane, 1.7 MAC (end-expired concentration: 0.8% in 65% N_2O, Normac™, Datex, Helsinki, Finland), and increments of fentanyl and pancuronium; and in the third group (isoflurane group, $n = 6$), halothane was replaced by an equipotent 1.7 MAC concentration of isoflurane (end-expired concentration: 1.3% in 65% N_2O).

During the surgical procedure, a liver biopsy was taken. Liver fragments were divided in two parts and immediately fixed. One part was fixed in Bouin's fluid and embedded in paraffin for light microscopy. Five-micron-thick sections were stained with hematoxyline-eosin and Masson's trichrome. The other part was cut in 1 mm^3 blocks, fixed in a solution of 2.5% glutaraldehyde in phosphate buffer 0.1M, pH 7.4, for 2 hr at 4°C. and, after washing in phosphate buffer, postfixed with 1.5% osmium tetroxide in veronal buffer pH 7.4 for 1 hr. After dehydration in graded ethanols, the blocks were embedded in epoxy resin for electron microscopy. One-micron semi-thick sections stained with toluidine blue were made on at least eight blocks for each biopsy. Ultrathin sections, stained with uranyl acetate and lead citrate, were examined with a Siemens Elmiskop 1A electron microscope. These morphological investigations were blindly made by two of us. Additionally to the ultrastructural routine study, morphometric investigation recording the morphologic aspects of some hepatocyte organelles was made for each patient in 30 randomly selected hepatocytes from two different blocks.

The ultrastructural changes specifically sought and quantitated microscopically in this investigation included dilation of the rough endoplasmic reticulum (RER), vesiculation of the smooth endoplasmic reticulum (SER), swelling of the mitochondria, irregularity of the nuclear membrane, and the presence of lysosomes. In each group of patients, 180 hepatocytes were randomly examined. The percentage of abnormalities in this population was calculated and statistical analysis (two-way analysis of variance) was made to compare differences in the frequency of cellular changes between the three groups. Data are expressed as mean ± SE. Differences were considered

Table 1. Clinical Data in the Three Groups of Patients

	Droperidol ($n = 6$)	Isoflurane ($n = 6$)	Halothane ($n = 6$)
Age (yrs)	50 ± 5	48 ± 6	49 ± 4
Weight (kg)	64 ± 2	61 ± 3	67 ± 6
Inhalation time before biopsy (min)		69 ± 10	65 ± 9
Systolic BP (mm Hg)	134 ± 9	122 ± 10	117 ± 5

Values represent mean ± SE. BP: blood pressure at the time of biopsy; n: number of patients in each group.

statistically significant if P values were less than 0.05.

Results

All the patients had normal liver biopsies on light microscopy. There were no significant differences among the three groups in the patients' age or weight and the time elapsing between the beginning of the halogenated agent administration and the biopsy (Table 1). There were no significant differences between the three groups of patients in the systolic blood pressure at the time of biopsy. No decrease in the systolic blood pressure under 90 mm Hg occurred in any patient before the biopsy.

The ultrastructural examination of hepatocytes in the three groups of patients showed that abnormalities of some cellular organelles could be observed. The comparison of abnormal hepatocytes (Figures 1B, 1C, and 1D) to normal hepatocytes (Figure 1A) demonstrated one or more changes in the same cell, the most obvious being a dilation of the RER (Figure 1B), vesiculation of the SER (Figures 1B and 1C), and the presence of numerous lysosomes (Figure 1D). Other abnormalities also observed included swelling of mitochondria (Figure 1C) and an irregular appearance of the nuclear membrane (not illustrated).

The RER dilation was most often moderate, reaching a part or the whole visible cisternae of the organelle. No changes in bound ribosomes were observed. The vesicular appearance of the SER was characterized by a moderate swelling of vesicles and tubules forming this organelle. Proliferation of the SER was not seen. The lysosomes took the appearance of small focal myelinic structures (Figure 1D).

The frequencies of these abnormalities in each group of patients are summarized in Table 2. Dilation of the RER and irregularities of the nuclear membrane were observed in all three of the groups of patients without any statistically significant difference be-
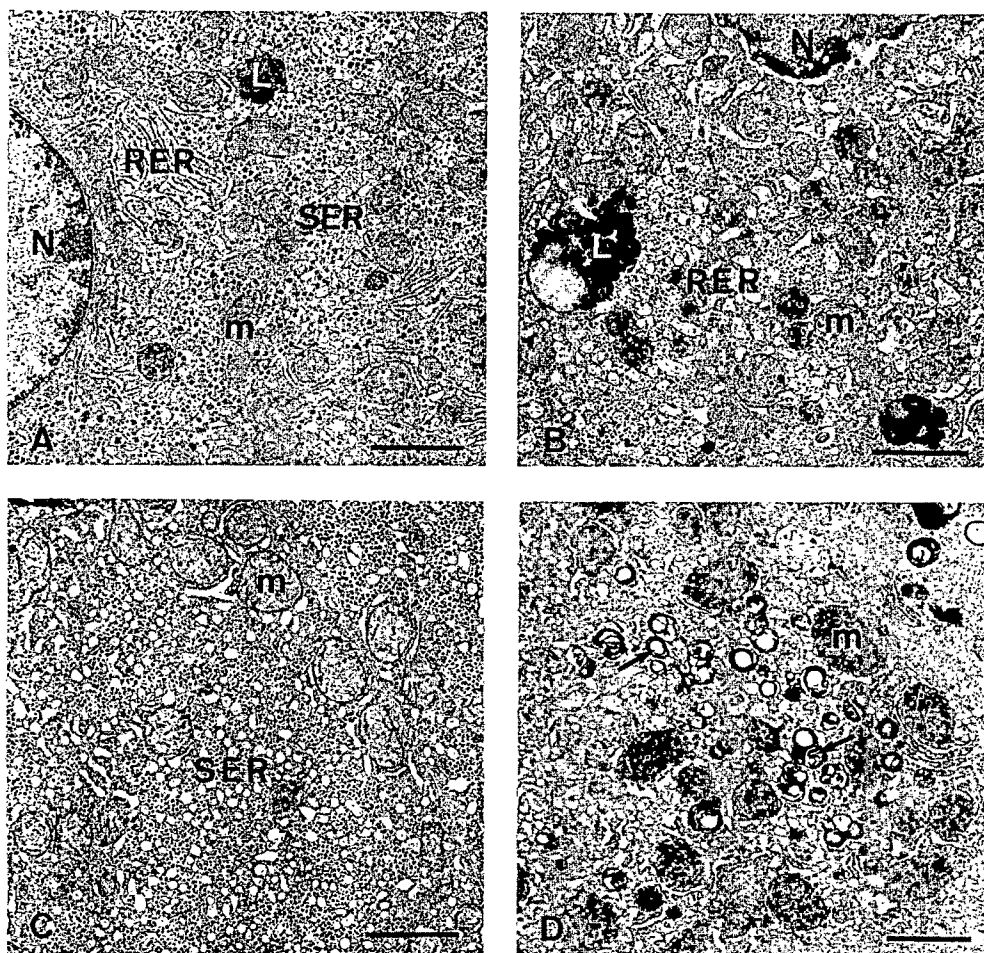
Table 2. Percentages of Hepatocytes with Organelle Abnormalities in Patients Having Droperidol, Isoflurane, or Halothane Anesthesia

	Droperidol ($n = 6$)	Isoflurane ($n = 6$)	Halothane ($n = 6$)
Dilation of RER	39 ± 13	40 ± 8	33 ± 12
Vesiculation of SER	30 ± 11	40 ± 9	56 ± 9
Irregular nuclear membranes	19 ± 4	20 ± 4	22 ± 5
Lysosomes	6 ± 3	5 ± 2	35 ± 10*
Mitochondria	5 ± 3	3 ± 3	2 ± 2

Values represent the mean ± SE of the percentages of hepatocytes showing organelles abnormalities in each patient. n: number of patients in each group; RER: rough endoplasmic reticulum; SER: smooth endoplasmic reticulum.

*Significantly different from isoflurane and droperidol groups ($P < 0.05$).

Figure 1. (A) Partial view of a normal hepatocyte; RER SER are not dilated. Mitochondria (m) are not swollen, and the nucleus (N) is round. (B, C and D) Partial views of three different hepatocytes with organelle abnormalities: a moderate dilation of RER (B); a vesicular appearance of SER (C); a moderate swelling of mitochondria (m) (C). The most obvious changes are the presence of numerous small lysosomes filled with membranous debris or myelinic figures (D) seen only in three patients in the halothane group. Lipofuchsin granules (L), lysosomes (→). Bars (2 μm).

tween them. Vesiculation of the SER was also observed in the three groups; it seemed to be more marked in liver biopsies obtained from patients given halothane without, however, any statistically significant difference among the three groups. Lysosomes were significantly increased in number in the halothane group when compared with the two other groups. There were no differences between the three groups involving the mitochondria.

Discussion

The purpose of the study was to compare in patients ultrastructural changes in hepatocytes during anesthesia with halothane or isoflurane.

It has been shown in animals that halothane can induce liver lesions visible on light microscopy, especially under certain experimental conditions such as enzyme induction, fasting, or hypoxia. Under the same experimental conditions, the lesions induced by isoflurane are absent or much less extensive than

those observed with halothane (7,10,11,13). Ultrastructural changes with halothane have also been reported, not only in animal but also in human hepatocytes. On electron microscopy, hepatocyte necrosis is characterized by several abnormalities of the endoplasmic reticulum, mitochondria, and lysosomes. The endoplasmic reticulum becomes disorganized and dilated; the mitochondria are swollen with an electron-lucent matrix; lysosomes are increased in number and in volume. In isolated rat hepatocytes, halothane also produces changes in plasma membranes that appear covered with numerous microvilli on scanning electron microscopy, while control hepatocytes remain spherical (14). In humans, halothane administration for 1 hr has been found to induce swelling and proliferation of both the rough and smooth endoplasmic reticulum, abnormal accumulation of lysosomes, and swelling of some mitochondria (12). These changes were observed in all the patients receiving halothane, suggesting that subtoxic histologic changes associated with halothane might be more frequent than commonly believed (1).

To our knowledge, the effect of isoflurane on the ultrastructure of hepatocytes has not been reported. Therefore, comparison of the effects of halothane and isoflurane on the ultrastructure of hepatic cells has not been previously made in humans. Theoretically it would have been better in this study to compare the histology of two liver biopsies in each patient, before and during anesthesia. However, for two reasons we felt we should examine only one liver biopsy. First, the complication rate of surgical liver biopsy, although exceptional, is not absent (15); second, in the present study, all the patients had normal liver function tests before surgery and there were no differences in the clinical characteristics between the three groups of patients. Therefore, the ultrastructural differences observed between the groups are very probably related only to the respective anesthetic agents employed to maintain anesthesia.

No significant differences were observed between the three groups in mitochondrial or nuclear aspects. The RER was not disorganized. Dilation of the RER and vesiculation of the SER were observed in all three groups of patients. Although vesiculation of the SER seemed to be more marked in patients given halothane, and, to a lesser extent, in patients given isoflurane, than in the droperidol group patients, as shown by the morphometric investigation (Table 2), no statistically significant differences were found between the three groups of patients.

The clinical significance of the changes in endoplasmic reticulum observed in this study is not clear, since they were also observed in more than 30% of

the hepatocytes of patients who did not receive inhalation anesthetics. The frequency of changes in the endoplasmic reticulum was higher in our patients given droperidol than reported by Sindelar et al. (12) in liver biopsies taken in patients with normal liver function tests before the operation. This difference could be related to the effect of surgery itself, especially in the upper abdomen, on the liver ultrastructure; laparotomy alone, for example, can decrease hepatic blood flow (3).

In our study, the main histologic abnormality involved lysosomes. Although in the present study liver biopsies were obtained only 1 hr after the beginning of inhalational anesthesia, there were ultrastructural differences between the patients given halothane and the patients given isoflurane or droperidol. In the halothane group, the number of hepatocytes containing lysosomes dramatically increased. Lysosomes are membrane-limited organelles containing numerous hydrolases. They degrade many membranes and organelles that have outlived their usefulness to the cell. The presence of such structures in the hepatocytes of patients given halothane suggests that halothane may induce cellular damages quite rapidly, even shortly after the beginning of its administration. The mechanism responsible for this rapid appearance of the ultrastructural changes cannot be determined from the present study. The low degree of halothane metabolism that could have occurred in but 1 hr during anesthesia suggests that a hypoxic mechanism may be involved, secondary to decreases in hepatic blood flow and oxygen availability reported with halothane (3). However, a toxic mechanism cannot be excluded, as production of toxic reductive metabolites of halothane may begin only a few minutes after the commencement of its administration (16). In our patients given halothane, changes observed in RER and lysosomes are roughly similar to those observed in a previous study with the same anesthetic agent (12). In the present study, accumulation of lysosomes in hepatocytes was not seen in liver biopsies of patients given isoflurane; this suggests that under the conditions we used, histologic changes are not seen with isoflurane. However, it cannot be excluded that under other conditions such as longer duration of the administration of isoflurane, additional changes of the organelles could be observed.

This study confirms that halothane can induce in the liver ultrastructural changes that differ quantitatively and qualitatively from those associated with isoflurane. Under the conditions of our study, changes in the ultrastructural appearance of the liver in patients given isoflurane were almost identical to

those seen in patients given intravenous anesthesia. Our results are an additional argument confirming that, with regard to hepatotoxicity, isoflurane is a better anesthetic agent than halothane.

References

1. Stock JG, Strunin L. Unexplained hepatitis following halothane. Anesthesiology 1985;63:424-39.

2. Schielbe TM, Costa AK, Heffel DF, Trudell JR. Comparative toxicity of halothane, isoflurane, hypoxia, and phenobarbital induction in monolayer cultures of rat hepatocytes. Anesthesiology 1988;68:485-94.

3. Gelman S. General anesthesia and hepatic circulation. Can J Physiol Pharmacol 1987;65:1762-79.

4. Legler DC, Van Dyke RA. Binding of halothane metabolites to rat liver microsomal lipid. Anesthesiology 1982;57:A218.

5. Krieter PA, Van Dyke RA. Halothane metabolism and cytochrome P-450 destruction. Anesthesiology 1981;55:A183.

6. Edmunds HN, Cohen EN, Trudell JR. Metabolite binding to liver nuclei during low level exposure to halothane. Anesthesiology 1979;51:S241.

7. Van Dyke RA. Hepatic centrilobular necrosis in rats after exposure to halothane, enflurane, or isoflurane. Anesth Analg 1982;61:812-9.

8. Zucker JR, Diamond EM, Berman MC. Effect of halothane on calcium transport in isolated hepatic endoplasmic reticulum. Br J Anaesth 1982;54:981-5.

9. Eger EI. Isoflurane: A review. Anesthesiology 1981;55:559-76.

10. Harper MH, Collins P, Johnson B, Eger EI, Biava C. Hepatic injury following halothane, enflurane, and isoflurane in rats. Anesthesiology 1982;56:14-17.

11. Gelman S, Rimerman V, Fowler KC, Bishop SP, Bradley EL. The effect of halothane, isoflurane, and blood loss on hepatotoxicity and hepatic oxygen availability in phenobarbital-pretreated hypoxic rats. Anesth Analg 1984;63:965-72.

12. Sindelar WF, Tralka TS, Gibbs PS. Evidence for acute cellular changes in human hepatocytes during anesthesia with halogenated agents: An electron microscopic study. Surgery 1982;92:520-7.

13. Fassoulaki A, Eger EI, Johnson BH, Ferrel LD, Smuckler EA, Cahalan MK, Eger RR, Harper MH. Isoflurane does not prevent hepatic injury produced by halothane in rats. Anesth Analg 1984;63:888-90.

14. Salhab AS, Nooh NG, Dujovne CA. Hepatocyte response to volatile anesthetics: Changes in surface scanning and enzyme leakage. Anesth Analg 1978;57:605-9.

15. Schultz F, Fritsch A. Hämobilie nach intraoperativer Leberpunktion. Dtsch Med Wochenschr 1980;105:645-9.

16. Gourlay GK, Adams JF, Cousins MJ, Sharp JH. Time-course of formation of volatile reductive metabolites of halothane in humans and in animal model. Br J Anaesth 1980;52:331-6.

Effect of Injection Rate on Level and Duration of Hypobaric Spinal Anesthesia

Scott R. Atchison, MD, Denise J. Wedel, MD, and Peter R. Wilson, MB BS, PhD

ATCHISON SR, WEDEL DJ, WILSON PR. Effect of injection rate on level and duration of hypobaric spinal anesthesia. Anesth Analg 1989;69:496–500.

The purpose of this study was to determine whether injection rate affects the spread of hypobaric spinal anesthesia. Hypobaric spinal anesthesia was performed on 20 patients for total hip arthroplasty. Dural puncture was performed with a 22-gauge Whitacre needle. All patients received 10 mg of hypobaric tetracaine with epinephrine. An electrically driven syringe pump was used to inject the anesthetic solution at either slow (250 sec) or fast (10 sec) rates. Ten patients received slow injections, and 10 received fast injections. Anesthetic levels, duration of anesthesia, and specific gravities of injectate and CSF were measured. Slow injection resulted in less spread of spinal anesthesia. Four-segment regression of anesthetic levels took significantly longer in the slow injection group. Local anesthetic mixtures used were consistently hypobaric compared to patient CSF. We conclude that slow injection of hypobaric tetracaine through a 22-gauge Whitacre needle produces lower levels of spinal anesthesia that tend to be of longer duration than levels resulting from fast injection.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—hypobaric. LOCAL ANESTHETICS, TETRACAINE.

Many factors affect the spread of intrathecally injected local anesthetic solutions. Two of the most important appear to be injectate specific gravity and patient position (1–4). Some authors have described clinical methods using specific gravity and patient position to control the spread of spinal anesthesia (5–7). Other factors considered are patient height, dural puncture site, needle type, direction of needle orifice, injectate volume, and local anesthetic dose (8–10). Little attention has been directed toward injection rate and its influence on spinal anesthesia. Neigh et al. examined the effect of injection rate on hyperbaric spinal anesthesia in 45 patients reporting some differences with fast injection (8). Several authors have commented on the observation that fast injection or barbotage results in more cephalad anesthesia levels than less vigorous injection (9–12). Apparently no one has examined the effect of very slow injection on spinal anesthestic spread. The experience of Kallos and Smith with repeated small injection of anesthetic solutions during continuous hypobaric spinal anesthesia suggested that lower spinal anesthesia levels could be achieved with incremental titrations of anesthetic solution (13). We designed this double-blind prospective study to investigate the effects of injection rate on the spread of hypobaric spinal anesthesia. We also measured onset and duration of anesthesia, hemodynamic effects, and transfusion requirements within the constraints imposed by our usual clinical practice and the surgical procedure.

Methods

Approval was obtained from our Institutional Review Board. Informed consent was obtained from 20 males, ranging from 173 to 183 cm in height, scheduled to undergo total hip arthroplasty. Exclusion criteria included the usual contraindications to regional anesthesia, previous hip surgery on the side of surgery, marked obesity, previous spinal surgery, and abnormal spinal anatomy (e.g., scoliosis). Patients were randomized into two groups—"fast" and "slow." Routine monitoring consisted of five-lead electrocardiography, blood pressure cuff, pulse oximetry (Nellcor®) and axillary temperature measurement (Yellow Springs Instrument). A loading infusion of 500 to 700 mL of lactated Ringer's solution was

administered before the induction of spinal anesthesia. Patients were positioned in the lateral decubitus position with the operative side uppermost (nondependent). The operating table was then adjusted in such a manner that a line between the L4 and T4 spinous processes was horizontal with the floor, as indicated by a fluid-filled tube used as a level. Lumbar puncture was performed using a 22-gauge Whitacre pencil-point lateral orifice needle at the L3–4 interspace via a midline approach. The Whitacre needle has a pencil-point; its orifice is located 2 mm proximal to the needle tip. We used only Whitacre needles because we wanted to control as many variables as possible. The laterally placed aperture allowed us to align consistently the orifice upward and perpendicular to the spine. Before injection, 5 mL of cerebrospinal fluid (CSF) was removed to maintain normal CSF volume after injection and for later analysis. Injection in every case consisted of tetracaine 10 mg and epinephrine 0.2 mg mixed in sterile water to make a volume of 5 mL. This 5 mL was injected at a rate of 0.5 mL/sec (10 sec) in the fast group. The injection rate was 0.02 mL/sec (250 sec) in the slow group. Injection was performed by an electrically driven syringe pump, specifically designed and built for this study, that was capable of delivering 5 mL at precise rates. The pump was connected to the needle by a 60 cm sterile pressure tubing (Mallinkrodt). The dead space of the delivery system was filled with the tetracaine solution, which was retained for subsequent analysis. Sensory dermatomal levels of anesthesia were assessed at 5-min intervals for 30 min following completion of injection. These assessments were made by an investigator who was blinded to the injection rate. Loss of "pinprick" sensation was used as a sensory endpoint for dermatomal sensory anesthesia. Regression of the block was determined in a similar manner. Time to regression was determined as that point at which the level of sensory anesthesia was found to have receded four dermatomes.

Specific gravity determinations were made on the injectate and CSF in each case. These determinations were made using a refractometer (American Optical) calibrated with distilled, deionized water at 25°C. All refractometric measurements were made at 25°C.

Electrocardiograms and blood pressures were monitored throughout the operation and in the immediate postoperative period. If the systolic blood pressure decreased to a level 30% below the patient's preoperative baseline level, lactated Ringer's solution and/or ephedrine sulfate in 12.5 mg intravenous doses were given. Bradycardia below 40 beats/min was treated with intravenous atropine in 0.4 mg
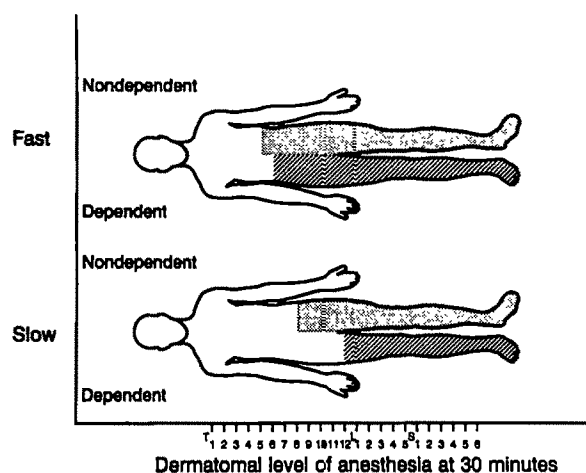
Figure 1. Schematic depiction of anesthesia levels at 30 min following injection. ▨ Mean nondependent anesthesia levels. ▧ Mean dependent anesthesia levels.

doses. Transfusion of packed red blood cells was administered according to measured loss and clinical judgment. Nausea was treated with intravenous droperidol when necessary.

Statistics

Differences in dermatomal levels of anesthesia, blood pressure, heart rate, and specific gravities of CSF and injectate were assessed using two-sample t-test comparisons. Transfusion requirements between "fast" and "slow" groups were compared by the rank-sum test. Differences lying outside of the 95% confidence level were accepted as significant.

Results

The groups were not different in height, weight, or age. Injection rate had a statistically significant influence on the spread of hypobaric spinal anesthesia. The maximum level of anesthesia on the nondependent (operative) side in the fast group was T4.5 ± 2.3 dermatomes (mean ± standard deviation) and on the dependent side was T5.7 ± 3.2 (Figure 1). Maximum nondependent and dependent levels in the slow group were $T_{8.7}$ ± 3.4 and $T_{12.4}$ ± 5.6, respectively (Figure 1). Thus cephalad spread of the level of anesthesia on both nondependent and dependent sides in the fast group was significantly greater than in the slow group ($P < 0.05$) (Figure 1). Also, nondependent levels were significantly higher than dependent levels within the slow group ($P < 0.05$) (Figure 1). No differences were found in levels of anesthesia
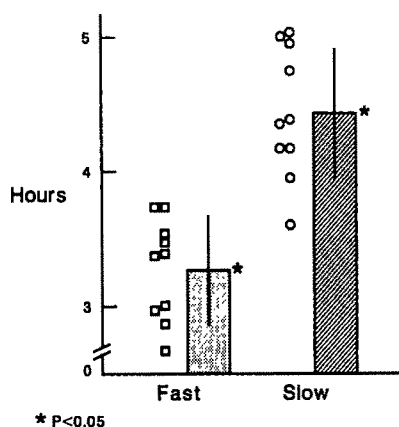
Figure 2. Time to four-segment regression from maximum levels of anesthesia on nondependent side. Open squares represent individual regression times in the fast group. Open circles represent individual regression times in the slow group. Shaded and stippled bars represent means with one standard deviation represented by error bars.

between nondependent and dependent sides in the fast group. Maximum levels of anesthesia occurred in every patient by 20 min following injection.

Time to four-segment regression, 266 ± 29.1 min, was longer in the slow group than in the fast group, 196 ± 22.3 min ($P < 0.01$) (Figure 2).

Injectate specific gravity, 1.001 ± 0.0003, was lower than patient CSF, 1.005 ± 0.0005, at 25°C ($P < 0.01$).

Pulse rates and blood pressures were no different between the two groups. Six patients in the fast group and seven patients in the slow group required atropine and/or ephedrine for bradycardia or hypotension.

Transfusions averaged 1.3 ± 0.82 units of packed red blood cells in the fast group and 2.3 ± 1.16 units in the slow group, a difference not statistically significant.

Discussion

Injection rate had a significant effect on the intrathecal spread of hypobaric tetracaine in this study. Rapid injection produced a bilateral spinal block with considerable cephalad spread. By contrast, slow injection produced lower levels of anesthesia with cephalad spread on the dependent side significantly less than on the nondependent side. Neigh et al. reported minimal differences in spread of hyperbaric tetracaine when injected at 1 mL/sec and 0.2 mL/sec (8). However, the volume of injectate in their study was 2 mL, making the difference between injection times only 9

sec. In our study the injection times differed by 4 min. Also, studies by Brown (1), Chambers (3), and Wildsmith (4) and their associates suggest that spread of anesthetic solutions is greater with hyperbaric than with isobaric or hypobaric solutions when the patient is in the horizontal position. Factors such as injectate viscosity and injection site (lumbar curve area) may influence such observed differences. Certainly gravity can affect spread of hypobaric solutions (5,13,14), and for that reason great care was taken in the present study to maintain a horizontal position to minimize the effects of gravity on spread.

Several factors may be responsible for the difference in spread between fast and slow injections. MacIntosh suggested that rapid injection may produce more turbulence at the needle orifice resulting in greater mixing and spread of the injectate with CSF in the spinal canal (11). The study by Neigh et al. of spread of hyperbaric tetracaine solutions using Whitacre needles also suggested that rapid injections may result in greater cephalad spread when the needle orifice is directed cephalad (8). In our study, the Whitacre needle orifice was always pointing toward the nondependent side, and thus the direction of the orifice cannot explain the observed difference in spread.

Spread of hyperbaric, isobaric, and hypobaric solutions in vivo and in vitro is determined by the baricity of the injectate (1-4). Baric gravity measurements of injectate and CSF confirm that our local anesthetic mixture was hypobaric in all cases. This holds true even if temperature differences between injectate (25° to 27°C) and CSF (37°C) are taken into account (14,15,17). In this study, slow injection yielded lower levels of anesthesia on the dependent side. Slow injection may allow more layering or separation of the hypobaric solution within the spinal canal by producing less turbulence. Injection through a Whitacre needle may enhance the effect of varying injection rate. We are unable to say whether similar results would occur with other types of needles. Slow injection may allow for some warming of the injectate as it passes through the needle and into the CSF. Warming could cause significant changes in injectate baricity. Davis demonstrated the importance of temperature in the consideration of specific gravity and baricity (16,18). Warming increases volume and decreases densities of solutions. Warming the injectate from 25°C to 37°C during injection could change the relative specific gravity as much as 0.0037 (16). Ernst demonstrated that 5 mL of injectate took approximately 3 min to achieve 37°C after injection (although speed of injection was not described) (19,20). In 1945,

Lund even advocated warming hypobaric tetracaine solution to 110°F prior to injection (21) to take advantage of this theoretical effect. More recently, Beardsworth and Stienstra demonstrated similar effects of warming on distribution of intrathecally injected local anesthetics (22,23).

Dermatomal anesthesia levels on the nondependent side persisted more than 1 hr longer in the "slow" group than the "fast" group. One important factor must be considered when interpreting this finding. We used time to four-segment dermatome regression of the spinal anesthesia level as our endpoint. Many patients still had adequate surgical levels of anesthesia after such regression. This was especially true in the fast group where spinal anesthesia reached higher levels. It is notable that even though slow injection produced lower levels of anesthesia, those levels were maintained for a longer time. Perhaps this is best explained by considering the relative dose of local anesthetic used to block each spinal segment. Fast injection spread the 10 mg of tetracaine over more dermatomes on both dependent and operative sides than did slow injection. Therefore, each blocked nerve root in the slow group theoretically was exposed to a higher dose of tetracaine than was each root in the fast group. This finding is not surprising; total dosage affects duration of spinal anesthesia (1,4,24,25), and it is likely that it accounts for the findings regarding duration in this study.

Elimination of local anesthetic may also be affected and lead to prolonged duration in the slow group. Lower anesthetic levels indicate a smaller volume of tissue distribution. This results in less surface area for vascular absorption of local anesthetic from its site of action. Therefore, delayed elimination may also contribute to the observed differences in duration between the fast and slow groups.

Sixty-five percent (13/20) of our patients required treatment with fluids, vagolytics, and/or sympathomimetics for reductions of heart rates and blood pressures 30% or more below baseline values. We could find no difference between the groups in regard to frequency of treatment or magnitude of effects. The majority of these patients were asymptomatic.

In summary, we found that very slow injection through an upwardly directed Whitacre needle affects spread. Warming of the injectate during slow injection may have contributed to some observed differences in spread. An additional finding was that the duration of anesthesia was greater in dermatomes blocked by slow injection. This is likely to be a result of the more limited spread of local anesthetic within

the spinal canal resulting in an increased concentration of local anesthetic in the nerve tissue and decreased surface area for elimination from the same tissue.

References

1. Brown DT, Wildsmith JAW, Covino BG, Scott DB. Effect of baricity on spinal anaesthesia with amethocaine. Br J Anaesth 1980;52:589–95.

2. Kitahara T, Kuri S, Yoshida J. The spread of drugs used for spinal anesthesia. Anesthesiology 1959;17:205–8.

3. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. Br J Anaesth 1981;53:279–82.

4. Wildsmith JAW, McClure JH, Brown DT, Scott DB. Effects of posture on the spread of isobaric and hyperbaric amethocaine. Br J Anaesth 1981;53:273–8.

5. Lund PC, Rumball AC. Hypobaric pontocaine spinal anaesthesia. 1,640 consecutive cases. Anesthesiology 1947;8:181–99.

6. Tanasichuk MA, Schultz EA, Matthews JH, Van Bergen FH. Spinal hemianalgesia: an evaluation of a method, its applicability, and influence on the incidence of hypotension. Anesthesiology 1961;22:74–85.

7. Louthan BW, Jones JR, Henschel EO, Jacoby J. Isobaric spinal anesthesia for anorectal surgery. Anesth Analg 1965;14:742–5.

8. Neigh JL, Kane PB, Smith TC. Effects of speed and direction of injection on the level and duration of spinal anesthesia. Anesth Analg 1970;49:912–8.

9. Greene NM. Physiology of Spinal Anesthesia. 2d ed. Baltimore: Williams and Wilkins Company, 1969:166.

10. Cousins MJ, Bridenbaugh PO. Neural Blockade in Clinical Anesthesia and Management of Pain. Philadelphia: J.B. Lippincott Company, 1980:156–7.

11. MacIntosh R. Cerebro-spinal fluid. In: Lumbar Puncture and Spinal Analgesia. 2d ed. Baltimore: Williams and Wilkins Company, 1957:33–42.

12. Moore DC. Regional Block. 4th ed. Springfield: Charles C. Thomas Publishers, 1981:157.

13. Kallos T, Smith TC. Continuous spinal anesthesia with hypobaric tetracaine for hip surgery in lateral decubitus. Anesth Analg 1972;51:766–73.

14. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. Anesth Analg 1985;64:715–30.

15. Davis H, King WR. Densities of common spinal anesthetic solutions at body temperature. Anesthesiology 1952;13:184–8.

16. Davis H, King WR. Densities of cerebrospinal fluid of human beings. Anesthesiology 1954;15:666–72.

17. Rosenberg H. Density of tetracaine-water mixtures and the effectiveness of 0.33 percent tetracaine in hypobaric spinal anesthesia. Anesthesiology 1976;45:682–4.

18. Davis H. Specific gravity of urine (letter). JAMA 1955;157:749.

19. Ernst EA. In vitro changes of osmolality and density of spinal anesthetic solutions. Anesthesiology 1968;29:104–9.

20. Ernst EA. Construction of a human spinal canal model. Anesthesiology 1967;28:939–41.

21. Lund PC, Cameron JD. Hypobaric pontocaine; A new technique in spinal anaesthesia. Anesthesiology 1945;6:565–73.

22. Beardsworth D, Datta S, Arthur GR, Lambert DH. The effect of temperature on the distribution of 0.5% plain bupivacaine in a simple spinal canal model. Reg Anesth 1988;13:25–8.

23. Stienstra R, van Poorten JF. The temperature of bupivacaine

0.5% affects the sensory level of spinal anesthesia. Anesth Analg 1988;67:272–6.

24. LeBeaux MI, Feldman HS, Covino BG. Effects of baricity and concentration of tetracaine solutions on experimental spinal anesthesia in sheep. Reg Anesth 1981;6:129–32.

25. Siker ES, Wolfson B, Stewart WD, Pavilack P, Pappas MT. Mepivacaine for spinal anesthesia: Effects of changes in concentration and baricity. Anesth Analg 1966;45:191–6.

501

Ketamine Does Not Trigger Malignant Hyperthermia in Susceptible Swine

Mark Dershwitz, MD, PhD, Frank A. Sréter, MD, PhD, and John F. Ryan, MD

The use of ketamine in individuals susceptible to malignant hyperthermia (MH) is controversial. We describe our experience with ketamine used for induction and/or maintenance of anesthesia in our herd of swine inbred for susceptibility to MH. A total of 76 MH-susceptible swine were given a total of 112 general anesthetics using ketamine as the induction drug. In 34 of these anesthetics, anesthesia was also maintained with ketamine. Signs of MH did not develop in response to ketamine in any of the pigs.

Key Words: HYPERTHERMIA, MALIGNANT. ANESTHETICS, INTRAVENOUS—ketamine.

In recent years, the list of anesthetics to be avoided in patients suceptible to malignant hyperthermia (MH) has been shrinking (1). Many of the drugs used in anesthesia, including lidocaine, curare, nitrous oxide (N_2O), and epinephrine, initially implicated as triggers of MH episodes, have now been recognized to be safe for the MH individual. Ketamine may still be considered a controversial anesthetic; it is a drug that is not routinely used with the MH-susceptible patient (2). The concern regarding the use of ketamine in MH may stem from its stimulatory effects on the sympathetic nervous system, which cause an increase in circulating catecholamine levels. While elevated blood levels of catecholamines accompany an MH episode, the infusion of catecholamines does not, by itself, trigger MH (3).

Although we have routinely employed ketamine via the intramuscular route as an induction anesthetic in our work with MH-susceptible swine, we have not experienced an untoward reaction to the drug. We describe here our experience with a total of 76 MH-susceptible pigs given 112 general anesthetics using ketamine as the induction drug. In 34 of the anesthet- ics, ketamine was also used for maintenance of anesthesia.

Methods

The study was approved by the Subcommittee on Animal Care of the Massachusetts General Hospital. A herd of Pietrain pigs, inbred for susceptibility to MH, was maintained at the research farm of the Boston Biomedical Research Institute and fed commercial pig chow ad libitum. Offspring of sows and boars known to be susceptible to MH were weaned at age 6–8 weeks. For determination of MH susceptibility, the following procedure was employed. The pig was given ketamine, 10 mg/kg, via an intramuscular injection in the rump. After approximately 10 min, a 22–24 gauge Teflon intravenous catheter was inserted into an ear vein without response from the pig, a normal saline infusion begun, and electrocardiogram (ECG) leads applied. The pig was then given 2% halothane and 67% N_2O in oxygen (O_2) by an anesthesia face mask, allowed to breathe spontaneously, and observed for signs of MH. The diagnosis of MH was made according to criteria previously described by Gronert and Theye (4).

Once an episode of MH occurred, the pig was given dantrolene, 1 mg/kg intravenously. This dose of dantrolene was repeated until the hind limbs were supple and vital signs had returned to normal values. The pigs were allowed to recover and, when awake, were returned to the farm.

Table 1. Responses of Swine Inbred for Susceptibility to MH to the Administration of Ketamine, Halothane, and Succinylcholine

Number of Inbred Pigs Tested for MH Susceptibility	78
Number of Halothane-positive Pigs	36 (46%)
Number of Halothane + Succinylcholine-positive Pigs	40 (51%)
Total Number of MH-susceptible Pigs	76 (97%)
Number of Pigs Nonresponsive to Halothane + Succinylcholine Challenge	2 (3%)
Number of Episodes of General Anesthesia Induced with Ketamine Administered to MH-susceptible Pigs	112
Number of Episodes of MH Occurring after Ketamine But before Halothane or Succinylcholine	0
Number of Episodes of General Anesthesia Induced and Maintained with Ketamine Administered to MH-susceptible Pigs	34
Number of Episodes of MH Occurring during Ketamine Anesthesia	0

We have employed MH pigs in 34 experiments in which the pigs' survival at the end of the experimental procedure—e.g., for obtaining blood samples, muscle biopsies, and electrophysiologic measurements—was desirable and an episode of MH undesirable. For such experiments, the pigs were administered ketamine intramuscularly, as described above, and given incremental doses of ketamine, 0.5 mg/kg intravenously, as needed to maintain cooperation, while breathing room air.

Results

Table 1 summarizes our experience with our inbred MH herd. We tested a total of 78 pigs for susceptibility to MH, and found that in 36 (46%) an MH episode was triggered when they breathed halothane alone, while another 40 (51%) required succinylcholine in addition to halothane in order to cause an episode of MH. All of the halothane-responders and 38 of the halothane-plus-succinylcholine-responders survived their MH episode. The two pigs that died after succinylcholine challenge suffered cardiac arrest and the absence of electrical activity on ECG shortly after succinylcholine administration, presumably as a result of succinylcholine-induced hyperkalemia. Two pigs failed to develop signs of MH after 15 min of halothane administration followed by succinylcholine (1 mg/kg).

None of the pigs developed any signs of MH in the interval between the administration of ketamine and halothane. In addition, 34 procedures were performed on known MH-susceptible pigs under ketamine anesthesia, again without any signs of MH.

Discussion

A number of literature reports have linked ketamine with the production of an MH episode. Mogensen et al. described MH episodes in two patients in whom anesthesia was induced with ketamine and who subsequently received also halothane and succinylcholine (5). Both patients had received halothane and succinylcholine during earlier anesthetics without developing MH, and the authors considered that the ketamine had been the agent to trigger the episodes. It is more likely that these case reports reflect the often observed phenomenon of an MH-susceptible individual in whom MH was not triggered during the first exposure to a known triggering agent.

Roervik and Stovner reported a child who developed fever and elevated creatine phosphokinase (CPK) levels after two separate operations for squint (6). She had been given halothane and succinylcholine for the first operation and had developed prolonged jaw rigidity after the administration of succinylcholine. Her serum CPK level on the first postoperative day was 1240 U/L (normal 15–78 U/L). The second operation was performed 6 months after the first, and she was given ketamine for induction and maintenance of anesthesia. At the end of the procedure, arterial blood gas data included a pH of 7.28, P_{CO_2} of 36 mm Hg, P_{O_2} of 145 mm Hg, and base excess $= -9.3$ mmol/L. Her serum CPK level was 67 U/L at the time of induction and 840 U/L on the second postoperative day. While the diagnosis of MH in this patient is likely, the causal effect of ketamine is unknown.

Lees and Macnamara described a child with Lowe's (oculocerebralrenal) syndrome who was given ketamine anesthesia for a muscle biopsy (7). He developed a tonic-clonic seizure and a fever to 39.8°, but no rigidity. The increase in temperature probably represents a postictal fever, not MH.

Cardan et al. presented a case that they described as MH following ketamine anesthesia (8). The patient had been given epidural anesthesia for an appendectomy. Because the epidural was ineffective, general anesthesia was induced with ketamine followed by succinylcholine. She subsequently developed a fever of 41.5°. Plasma CPK levels peaked on the second postoperative day at 1140 U/L (normal < 50 U/L). The use of succinylcholine and the expected febrile response to appendicitis obscure the diagnosis of the causes of fever in this patient.

Rasore-Quartino et al. related a fatal episode of MH in a child who underwent muscle biopsy for diagnosis of myopathy (9). His illness was characterized by hypotonia, ptosis, inability to ambulate, and

the absence of muscular hypertrophy. Because an intravenous catheter could not be inserted, the patient was premedicated with atropine and meperidine and then given ketamine for the surgery, all intramuscularly. The patient did not awaken; he developed fever, metabolic acidosis (lowest pH was 7.15, 44 hr postoperatively), and elevated CPK levels (4700 U/L, normal 10–70 U/L). Initially he was hypotonic, but developed muscle hypertonia 29 hr postoperatively. He died 60 hr after surgery. The delay in the development of rigidity, in combination with the reported metabolic abnormalities and associated coma, suggests that the rigidity was a result of some unidentified central nervous system (CNS) or metabolic pathology.

No other cases of MH linked to ketamine usage have been reported. Considering the frequency with which it is applied in anesthesia and the prevalence of susceptibility to MH, if ketamine were capable of acting as a trigger for MH, it is most likely that such cases would have been described by now.

There are also reports of the safe use of ketamine in potentially MH-susceptible individuals. Wadhwa and Tantisira described a patient with an elevated resting CPK level and a brother who had died from MH. The patient was given ketamine anesthesia for a parotidectomy (10). Meltzer et al. showed that ketamine does not increase CPK levels in normal human volunteers (11), while Harrison et al. reported that in five MH-susceptible pigs, where MH had been triggered with halothane, anesthesia had been safely induced with ketamine (12).

Our data support the contention that ketamine is a safe anesthetic agent in the MH-susceptible individual. The pig is an excellent model for human MH, and drugs shown to be capable of triggering MH in the pig have done so in susceptible humans. The two MH-susceptible pigs in our series who did not develop MH following exposure to halothane and succinylcholine exemplify the similarity between pigs and humans in that MH does not develop in the presence of MH susceptibility during every exposure to MH-triggering drugs.

In the literature reviewed above, only the case reported by Roervik and Stovner describes an episode that was likely to be MH and in which no other causative anesthetic is apparent. Because of the age of this report, it is impossible to determine whether there were complicating factors present, such as residual halothane in the anesthetic system. There are two reports, however, of known MH-susceptible patients who were pretreated with dantrolene and yet experienced MH episodes under general anesthesia, even though no known trigger had been administered (13,14).

When ketamine is the agent of choice for a particular procedure in an MH-susceptible patient, it may be used. Since even the pretreatment with dantrolene and the use of nontriggering drugs has been associated with the development of MH, the anesthesiologist must be as vigilant as possible in monitoring the patient. The use of end-tidal carbon dioxide (15,16) and oxygen saturation monitoring is especially valuable. The anesthesiologist must be alert to the rare but possible occurrence of MH and ensure the immediate availability of dantrolene for MH-susceptible patients.

References

1. Gronert GA. Malignant hyperthermia. In: Miller RD, ed. Anesthesia, 2nd ed. New York: Churchill Livingstone, 1986:1971–94.

2. Gronert GA, Malignant hyperthermia. Anesthesiology 1980; 53:395–423.

3. Gronert GA, White DA. Failure of norepinephrine to initiate porcine malignant hyperthermia. Pflugers Arch 1988;411:226–8.

4. Gronert GA, Theye RA. Halothane-induced porcine malignant hyperthermia: metabolic and hemodynamic changes. Anesthesiology 1976;44:36–43.

5. Mogensen JV, Misfeldt BB, Hanel HK. Preoperative excitement and malignant hyperthermia. Lancet 1974;1:461.

6. Roervik S, Stovner J. Ketamine-induced acidosis, fever, and creatine-kinase rise. Lancet 1974;2:1384–5.

7. Lees DE, Macnamara T. Ketamine-induced hyperthermia: postictal or malignant? Anesthesiology 1977;47:390–1.

8. Cardan E, Balogh A, Cucuianu M. A case of malignant hyperthermia. Rev Chir [Chir] 1984;33:77–80.

9. Rasore-Quartino A, De-Bellis P, Bertamino F, Rovei S. Atypical form of malignant hyperthermia. Observation of a case caused by ketamine. Pathologica 1985;77:609–17.

10. Wadhwa RK, Tantisira B. Parotidectomy in a patient with a family history of hyperthermia. Anesthesiology 1974;40:191–4.

11. Meltzer HY, Hassan SZ, Moretti R, Hengeveld C, Bruckner D. Effect of ketamine on creatine phosphokinase levels. Lancet 1975;1:1195–6.

12. Harrison GG, Morell DF, Brain V, Jaros GG. Acute calcium homeostasis in MHS swine. Can J Anaesth 1987;34:377–9.

13. Fitzgibbons DC. Malignant hyperthermia following preoperative oral administration of dantrolene. Anesthesiology 1981; 54:73–5.

14. Ruhland G, Hinkle AF. Malignant hyperthermia after oral and intravenous pretreatment with dantrolene in a patient susceptible to malignant hyperthermia. Anesthesiology 1984;60:159–60.

15. Baudendistel L, Goudsouzian N, Coté C, Strafford M. End tidal CO_2 monitoring. Its use in the diagnosis and management of malignant hyperthermia. Anaesthesia 1984;39:1000–3.

16. Dunn CM, Maltry DE, Eggers GWN. Value of mass spectrometry in early diagnosis of malignant hyperthermia. Anesthesiology 1985;66:333.

Smooth Muscle Contraction and Local Anesthetics: Calmodulin-Dependent Myosin Light-Chain Kinase

Shuichi Nosaka, MD, PhD, Hiroshi Kamaya, MD, PhD, Issaku Ueda, MD, PhD, and K.C. Wong, MD, PhD

NOSAKA S, KAMAYA H, UEDA I, WONG KC. Smooth muscle contraction and local anesthetics: Calmodulin-dependent myosin light-chain kinase. Anesth Analg 1989;69:504-10.

Myocardial depressant action of local anesthetics at toxic concentrations is well documented. Their effect on vascular smooth muscle, however, remains controversial. This study analyzed local anesthetic action on the subcellular smooth-muscle contractile system. Highly purified smooth-muscle myosin and myosin light-chain kinase (MLCK) were prepared from fresh turkey gizzards, and the phosphorylation of the myosin light-chain in the presence of Ca^{++} and calmodulin was evaluated by the urea gel-electrophoresis. Tetracaine $1.3 \cdot 10^{-3}$ M and bupivacaine $7.5 \cdot 10^{-3}$ M inhibited the MLCK 50%, whereas lidocaine $2.5 \cdot 10^{-2}$ M inhibited the MLCK 40%. The inhibitory action was partially reversed by increasing the calcium ion concentration from $1 \cdot 10^{-5}$ to $2 \cdot 10^{-4}$ M. On the other hand, raising the calmodulin concentration from $1 \cdot 10^{-7}$ M to $6 \cdot 10^{-7}$ M completely reversed the inhibition. A possible cause of the discrepancy in the anesthetic concentrations between subcellular and in vivo studies is discussed.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine, tetracaine. MUSCLE, SMOOTH—local anesthetic effects.

Despite the general notion that local anesthetics antagonize Ca^{++} ion induced muscular contraction and thus relax smooth muscles (1–4), direct demonstrations of the inhibitory effect of local anesthetics on the smooth-muscle contractile system are few. Reports on the excitation-contraction coupling (E-C coupling) at the sarcoplasmic reticulum (SR) are limited to the SR membranes prepared from striated muscles, including myocardium (5–10).

While tension development in all muscle is controlled by intracellular calcium ion, the smooth-muscle contractile system is different from that in striated muscles (11–14). In smooth muscle, the ultrastructure lacks the regularity of actin and myosin strata, and the A-band, I-band, and Z-line, which are characteristic of the striated muscle. In striated mus-

cle, the accessibility of actin to myosin for tension development is modulated by Ca^{+-} binding to the troponin-tropomyosin complex that resides on the actin filaments. In smooth muscle, however, the myosin head must be transphosphorylated from ATP before myosin becomes receptive for binding actin (11–14). The phosphorylation occurs in the 20,000 dalton light-chain (the phosphorylatable light-chain) by the action of the myosin light-chain kinase (MLCK) in the presence of Ca^{++} and calmodulin. Figure 1 shows simplified diagrams for the striated and smooth-muscle contractile systems.

This study analyzes the effects of local anesthetics on the transphosphorylation of highly purified smooth-muscle myosin from ATP, catalyzed by the calmodulin-dependent myosin light-chain kinase. Effects of local anesthetics on the actin portion (globular to filamentous transformation) of the actin-myosin complex will be the subject of our forthcoming report.
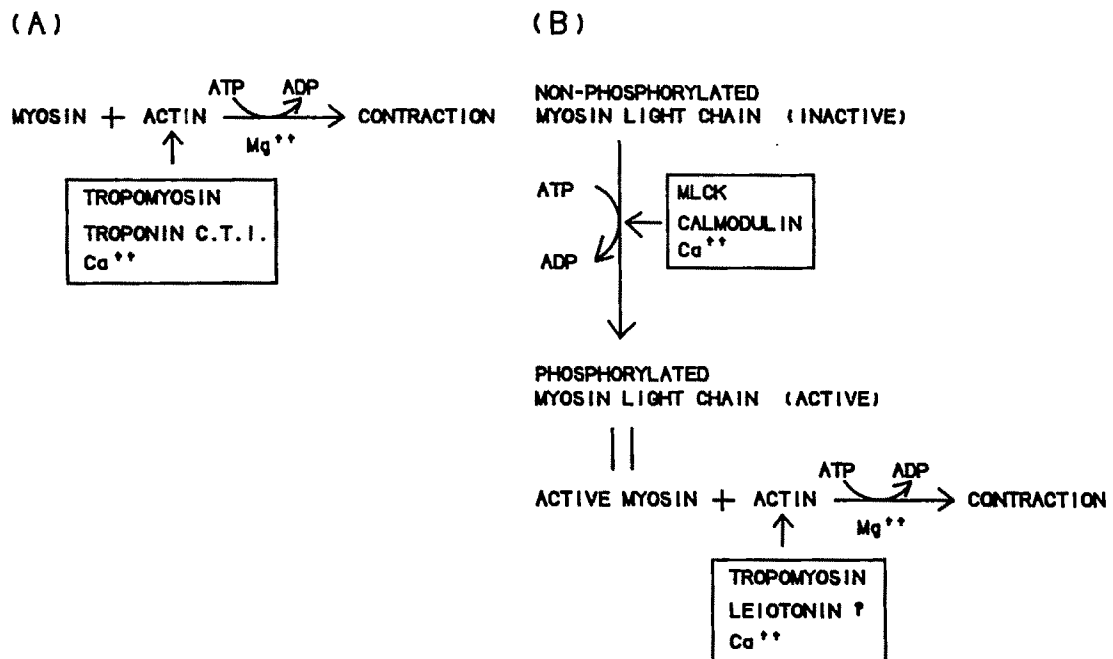
Methods

Because smooth-muscle myosin light-chains are essentially invariant among the various smooth muscles (see a review by Small and Sobieszek (11)), highly

(A)

(B)

MYOSIN + ACTIN $\xrightarrow{\text{ATP} \quad \text{ADP}}$ CONTRACTION

$\uparrow$ Mg^{++}

TROPOMYOSIN
TROPONIN C.T.I.
Ca^{++}

NON-PHOSPHORYLATED
MYOSIN LIGHT CHAIN (INACTIVE)

ATP

ADP

MLCK
CALMODULIN
Ca^{++}

PHOSPHORYLATED
MYOSIN LIGHT CHAIN (ACTIVE)

| |

ACTIVE MYOSIN + ACTIN $\xrightarrow{\text{ATP} \quad \text{ADP}}$ CONTRACTION

$\uparrow$ Mg^{++}

TROPOMYOSIN
LEIOTONIN ?
Ca^{++}

Figure 1. Muscle contraction. A: Skeletal muscle. B: Smooth muscle. In the skeletal muscle, the sliding between actin and myosin is initiated by the change in the actin molecule induced by tropomyosin, troponin C (calcium binding subunit), troponin I (inhibitory subunit), troponin T (tropomyosin-binding subunit) and calcium ion. In the smooth muscle, the conjugation occurs only after the myosin is activated by MLCK to form phosphorylated myosin. The function of smooth-muscle tropomyosin is not well understood, and the presence of troponin is unclear. In the figure, leiotonin is mentioned, because this protein was reported to function as troponin counterpart in the vascular smooth muscle (29). The contraction occurs between the activated myosin molecule and the actin molecule in the presence of tropomyosin and calcium ion. The muscle contraction is accompanied by an increase in the Mg^{++}-ATPase activity.

purified myosin was prepared from turkey gizzards. Fresh gizzards were obtained from a local poultry farm and carried to the laboratory in ice. About 120 g of gizzards was processed at one time. The gizzards were minced twice with a meat grinder. The minced material was mixed with 3 volumes of 50 mM KCl, 15 mM MgCl$_2$, 2 mM EGTA, 3% Triton X-100 (v/v), 0.5 mM dithiothreitol, 0.2 mM phenylmethylsulfonyl fluoride, and 10 mM Tris-Cl buffer pH 7.5. The mixture was homogenized and myosin was purified according to the method described by Dabrowska et al. (15). The method takes advantage of myosin polymerization in the absence of ATP and depolymerization in the presence of a high concentration of ATP. It consists of a series of ultracentrifugations in the absence of ATP to precipitate the protein and in the presence of ATP to solubilize it. Each step is followed by extensive dialysis. The obtained myosin was free from myosin light-chain kinase and was the inactive type (nonphosphorylated light-chain, see results). Starting from about 120 g turkey gizzards, the yield was 170 mg. The protein concentration was measured by spectrophotometry at 595 nm after mixing with BioRad protein assay reagent, consisting of Coomassie Brilliant Blue G-250, phosphoric acid, and ethanol, using bovine serum albumin as the standard, according to the method described by Bradford (16). The purified myosin was used within 4 days after preparation.

The myosin light-chain kinase was prepared from the turkey gizzard homogenate by ammonium sulfate fractionation between 40 and 60% saturation according to the method of Adelstein and Klee (17). The ammonium sulfate precipitate was collected by centrifuging 15,000 g, and dissolved in 0.6 M KCl, 1 mM EGTA, and 10 mM Tris-Cl buffer pH 7.5. The material was dialyzed 24 hr against the same buffer. The dialyzed solution was centrifuged at 11,000 g and the precipitate was discarded. The supernatant was stored at −80°C until use.

The MLCK activity was determined by the degree of phosphorylation of the smooth-muscle myosin light-chain in the presence of ATP, calcium ion, and calmodulin. The standard assay mixture contained the purified myosin 75 μg, the MLCK fraction 30 μg, calmodulin 0.2 μg, 1.0 mM ATP, 1.0·10^{-5} M CaCl$_2$, 5.0 mM MgCl$_2$, 80 mM KCl, and 20 mM Tris-malate buffer pH 6.8 in a total volume of 100 μL. The reaction was started by the addition of ATP at 22°C and stopped after 5 min by adding solid urea to a final concentration of 8 M. The reacted myosin was dis-
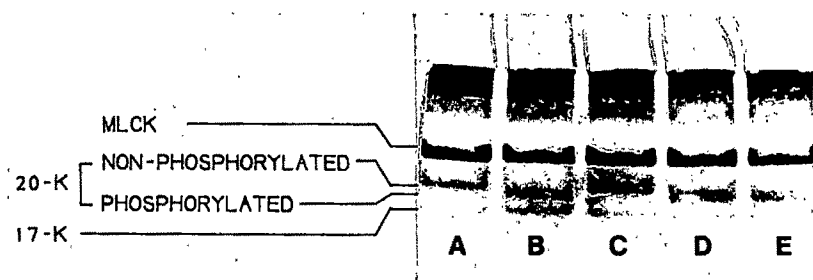
Figure 2. Urea polyacrylamide gel, stained by Coomassie blue. A: Control myosin without ATP. The 20-K light chain is in a single band, showing that the preparation is free from contamination of phosphorylated myosin. B: Control myosin after interaction with MLCK, calcium, calmodulin and ATP. The 20-K light-chain is phosphorylated and the band splits into two: phosphorylated and nonphosphorylated portions. The position of the 17-K light chain is unchanged. C: Inhibition by tetracaine 5.0 mM. The phosphorylation of the 20-K light chain is completely suppressed and the band position is identical with the slab A. D: Tetracaine 1.0 mM. The phosphorylation is partially inhibited. From the ratio between the densities of phosphorylated and nonphosphorylated subunits measured by the integrating Laser gel-scan densitometer, the magnitude of inhibition is estimated. E: Tetracaine 0.5 mM. Similar to D.

solved in a solution consisting of (final concentrations) Tris 120 mM/glycine 750 mM (Tris-glycine buffer pH 8.3) glycerol 30% (v/v), and 2-mercaptoethanol 10% (v/v).

The myosin phosphorylation was determined by the urea polyacrylamide gel electrophoresis described by Chacko and Rosenfeld (18) using a Mini Protein II (BioRad) and a Model 3000Xi microprocessor-controlled Power Supply (BioRad). The gel was 13.8% acrylamide with 40 mM Tris/250 mM glycine buffer pH 8.3, 7 M urea, ammonium persulphate 0.05% (w/v) and N,N,N',N'-tetramethylethylenediamine 0.1% (v/v). The electrophoresis buffer was 40 mM Tris/250 mM glycine buffer pH 8.3. An aliquot of the urea-dissolved myosin was applied to the gel in a final concentration of 24 mM Tris/150 mM glycine buffer pH 8.3, 6% (v/v) glycerol, 2% (v/v) 2-mercaptoethanol, bromothymol blue 0.02% (w/v) and 8 M urea.

Gels were stained by 0.1% Coomassie blue in 50% methanol and 10% acetic acid mixture. They were destained by 10% methanol and 10% acetic acid mixture. The destained gel slabs were dried in a BioRad Model 443 Slab Dryer 3 hr at 80°C under reduced pressure. The band intensity in the dried gel was measured by an integrating LKB Ultrascan Laser Densitometer (Bromma, Sweden) interfaced with an Apple II microcomputer. The degree of the light-chain phosphorylation was estimated from the ratio of the band intensities between phosphorylated and nonphosphorylated 20-K light chain.

Lidocaine was supplied from Astra (Worcester, MA). Tetracaine and bupivacaine were obtained from Sigma (St. Louis, MO). These local anesthetics were in the hydrochloric acid salt form. The pH of the reaction mixture was determined after the addition, and the pH was readjusted by Tris-malate buffer pH 6.8, when required. Calmodulin was obtained from

BioRad (Richmond, CA). All other reagents were of the highest grade available.

Local anesthetics were added to the standard assay mixture at an appropriate concentration. Assay of the MLCK activity was repeated at least five times at each anesthetic concentration, and the data were presented by the mean plus standard error. The significance of the inhibition was estimated by Student's t-test after validating the equality of variances in each population by the F-distribution. The differences in the effects among three anesthetics were checked by the analysis of variance by comparing the data scatters within and between the groups.

Results

Figure 2 shows the typical gel slab stained by Coomassie blue after electrophoresis. The reaction mixture was treated with high concentration of urea to dissociate the light-chain subunits from the myosin proper. The 17-K subunit migrates faster than the 20-K subunit.

Figure 2A is the control in the absence of ATP. The 20-K protein shows a single band, indicating that the preparation was essentially free from contamination of the phosphorylated form. Figure 2B is the control after interaction with MLCK with calcium, calmodulin, and ATP, in the absence of local anesthetics. The 20-K light-chain protein was transphosphorylated from ATP and split into two bands: phosphorylated and nonphosphorylated. The phosphorylated band migrated farther compared to the nonphosphorylated band, whereas the position of the 17-K band did not change (Figure 2A).

Figures 2C, D, and E show inhibition of the phosphorylation of the light-chain by tetracaine at 5.0 mM, 1.0 mM, and 0.5 mM, respectively. At 5.0 mM
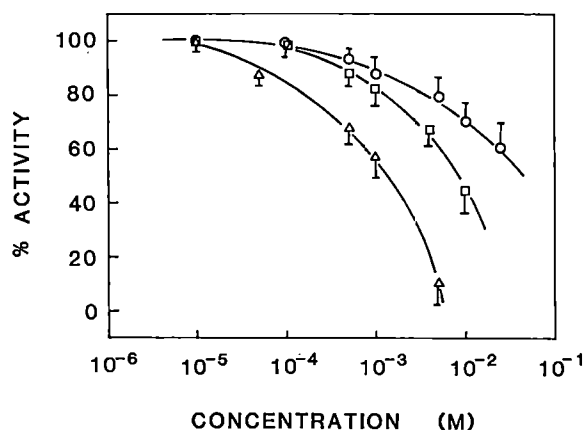
Figure 3. Dose-response curve of local anesthetic inhibition of MLCK. The MLCK activity is expressed by the percentage of the control activity without anesthetics. Data points are the average of five observations with standard error bars. Inhibitions are statistically significant ($P < 0.05$) above 0.05 mM for tetracaine, and above 1.0 mM for bupivacaine and lidocaine. Ordinate: relative MLCK activity expressed by percent of the control. Abscissa: concentration of drugs in logarithmic scale. Symbols: lidocaine O, bupivacaine □, and tetracaine △.
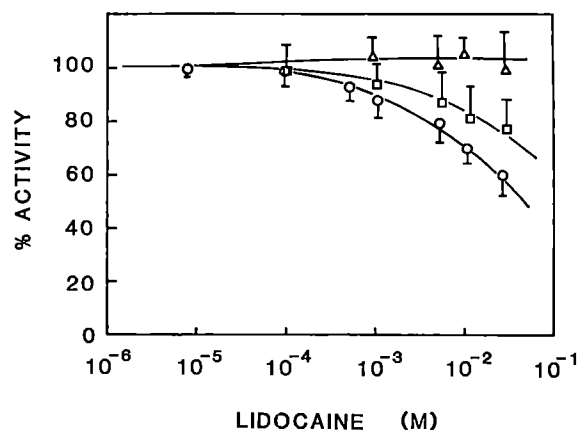

Figure 4. Antagonism by calcium ion $2 \cdot 10^{-4}$ M and calmodulin $6 \cdot 10^{-7}$ M against lidocaine inhibition on the MLCK activity. Complete recovery of MLCK activity is observed with the increase in the calmodulin concentration, but only partial recovery is observed with calcium ion. Ordinate: relative MLCK activity expressed by percent of the control. Abscissa: lidocaine concentrations in logarithmic scale. Symbols: control (Ca^{++} $1 \cdot 10^{-5}$ M and calmodulin $1 \cdot 10^{-7}$ M) O, Ca^{2+} $2 \cdot 10^{-4}$ M (calmodulin $1 \cdot 10^{-7}$ M) □, and calmodulin $6 \cdot 10^{-7}$ M (Ca^{2+} $1 \cdot 10^{-5}$ M) △.

tetracaine concentration, the phosphorylation was completely inhibited: the position of the 20-K light-chain band was identical with Figure 2A, where the 20-K light-chain was not phosphorylated. At 1.0 and 0.5 mM tetracaine concentration, the 20-K band split into two bands. From the ratio between the densities of the phosphorylated and nonphosphorylated bands, the magnitude of the inhibitory effect was estimated.

The inhibition by local anesthetics was in the order of tetracaine > bupivacaine > lidocaine. Figure 3 is the dose-dependent inhibition of the MLCK activity expressed by the degree of the myosin light-chain phosphorylation. Tetracaine $1.3 \cdot 10^{-3}$ M and bupivacaine $7.5 \cdot 10^{-3}$ M inhibited the MLCK activity 50% while lidocaine $2.5 \cdot 10^{-2}$ M inhibited the MLCK only 40%. These inhibitory effects of local anesthetics were partially reversed by increasing the calcium ion concentration from $1 \cdot 10^{-5}$ to $2 \cdot 10^{-4}$ M. In contrast, an increase in the calmodulin concentration from $1 \cdot 10^{-7}$ to $6 \cdot 10^{-7}$ M almost completely antagonized the anesthetic depression. When calmodulin was omitted, the MLCK activity was completely suppressed. Figure 4 shows the effect of increased calcium ion and calmodulin on the phosphorylation reaction in the presence of lidocaine.

Discussion

With tetracaine, inhibition of the MLCK activity became significant ($P < 0.05$) above $5 \cdot 10^{-5}$ M, whereas the concentrations of bupivacaine and lidocaine for

significant inhibition were above $1.0 \cdot 10^{-3}$ M. Analysis of variance of the anesthetic effects at $1.0 \cdot 10^{-3}$ M showed that the difference among three anesthetics was significant at $P < 0.01$. Because lidocaine failed to inhibit the MLCK activity 50% under the present experimental condition, the inhibitory actions were compared at 40% inhibition level. The 40% inhibition concentrations were: tetracaine $7.8 \cdot 10^{-4}$ M, bupivacaine $5.0 \cdot 10^{-3}$ M, and lidocaine $2.5 \cdot 10^{-2}$ M. The tetracaine:bupivacaine:lidocaine potency ratio was 31:5:1. This potency ratio correlates better to their hydrophobicity expressed by the oil solubility ratio than to the nerve-blocking potency ratio. Savarese and Covino (19) listed that the tetracaine:bupivacaine:lidocaine ratio as 27.6:9.7:1 for the lipid solubility and 4:4:1 for the in vitro nerve blocking potency. Rigorous comparison against the nerve blocking potency, however, may be impractical because the nerve blocking concentration varies according to the experimental condition, e.g., voltage dependence or frequency dependence.

Local anesthetic actions on smooth-muscle contractility have been investigated at tissue and cellular levels with conflicting results. Numerous reports exist on the spasmolytic action of local anesthetics (see a review by Feinstein and Paimre (3)). They stated that local anesthetics are nonspecific inhibitors of smooth muscle contraction and showed that anesthetic concentrations that induce half maximal inhibition of contractility are nearly equal for all contractions induced by various agonists in a wide variety of tissues, e.g., rabbit aorta, rat uterus, rabbit and guinea pig taenia coli, and guinea pig ileum. The

inhibitory effect is attributed to the antagonism between local anesthetics and Ca^{++}. The inhibitory action of local anesthetics on smooth-muscle contraction was also found in electrically stimulated tissues. Increasing the Ca^{++} concentration only partially reverses the inhibition, while washout of the anesthetics completely reverses it (3).

Against these relaxation data, Åberg and Wahlström (20) reported biphasic response of isolated rat portal vein to mepivacaine. They showed that the initial response was constriction that converted to relaxation about 10 min after application. The relaxation proceeded more rapidly at higher anesthetic concentrations.

In vivo studies are also confusing. Nishimura et al. (21) reported that injection of local anesthetics (procaine, lidocaine, prilocaine, mepivacaine, tetracaine, and dibucaine) into dog femoral artery increased the blood flow to the hind leg, whereas cocaine decreased the blood flow. In contrast, Johns et al. (22,23) reported vasoconstriction by low concentrations of lidocaine and bupivacaine when applied on the exposed surface of microvasculature of rat scrotum. At higher concentrations, lidocaine dilated the arterioles, but the dilatory action of bupivacaine was marginal. They (22,23) concluded that relaxation of vascular system is irrelevant to cardiovascular toxicity. Their results contradict the report of Åberg and Wahlström (20) who found that bupivacaine, in contrast to mepivacaine, always relaxed isolated rat portal veins and did not increase the tension at any concentrations. The cause of this difference between the two studies is unclear. Johns et al. (22,23) suggested that irritative effects of local anesthetics or a reflex secondary to systemic effects may be possible causes for the arteriolar contraction.

The local anesthetic concentrations in the present study exceed nerve blocking concentrations. The relationship between these high concentrations and the concentrations associated with in vivo cardiovascular collapse is not clear. Measured anesthetic concentrations in blood at the time of cardiovascular collapse may not be comparable with drug concentrations inhibiting enzymes in smooth-muscle function seen in in vitro studies. The measured anesthetic content in blood is the unbound concentration, or the leftover after tissue binding, whereas in the subcellular system, the quantity represents total (bound plus free) concentrations. Because partition coefficients between organic phase and water are high and the mass of the binding tissue is not known, the concentration of local anesthetics in tissue at the time of local anesthetic cardiovascular collapse cannot be defined. The effective concentrations of local anesthetics

that inhibit subcellular muscular contractile system appear to be always greater than those that block muscular contraction in isolated tissues or in vivo studies. For example, Lynch (24) reported the concentrations of local anesthetics that depressed contractile strength of the isolated papillary muscle were 4 μM for bupivacaine and etidocaine, and 40 μM for lidocaine. On the other hand, the concentrations of local anesthetics required to affect Ca^{++} translocation in isolated sarcoplasmic reticulum are substantially higher. Katz et al. (8) found that in canine cardiac fragmented sarcoplasmic reticulum 10 mM lidocaine inhibited only 20% of ATP-dependent Ca^{++} transport, and 50% inhibition was achieved by 2.5 mM tetracaine and 0.75 mM dibucaine. Similarly, Wilcox and Fuchs (6), in their study of the effects of local anesthetics on sarcotubular calcium transport of rabbit skeletal muscle, found that 50% inhibition was produced by dibucaine 0.4 mM, by tetracaine 0.8 mM, by lidocaine 15 mM, and by procaine 20 mM. The requirement of millimolar range of local anesthetic concentration is common in subcellular systems for Ca^{++} antagonism (5–10).

Reasons for the large difference in the effective concentrations of local anesthetics between in vivo and subcellular studies are complex and not completely known. Drug concentrations, however, may often be deceptive because drug effect is proportional to the activity of the drug and not to its concentration. Drug activity is related to the concentration by the activity coefficient, which is widely variable depending on experimental conditions. The negative charges on the surface of cell membranes can concentrate positively charged local anesthetics up to 150-fold at the membrane surface (see Appendix). Of course, this figure varies according to the charge density of the cell membranes, buffer, electrolyte concentrations, dielectric constant of the binding site, among other things.

Reports are accumulating on the inhibitory actions of local anesthetics upon various calmodulin-dependent enzymes (25–28), e.g., membrane-bound guanylate cyclase, cyclic nucleotide phosphodiesterase, $(Ca^{++} + Mg^{++})$-ATPase, and MLCK. In these studies, inhibitory actions were found to be caused by direct interaction between local anesthetics and calmodulin. The local anesthetic inhibitions on these enzymes occurred in millimolar range and were antagonized completely by increasing the calmodulin concentration but only partially by increasing Ca^{++} concentrations. The present results agree with these findings.

It has been postulated (25–28) that the association of calcium ion with calmodulin initiates conforma-

tional changes of calmodulin and exposes a hydrophobic domain in the calmodulin molecule to outside. The exposed hydrophobic domain conjugates with calmodulin-dependent regulatory proteins such as MLCK. This mechanism appears to be the main step for the activation of calcium-calmodulin system to interact with protein kinases. Anesthetic molecules may bind to the hydrophobic domain of calmodulin and prevent its action. It has been suggested (25–28) that the inhibitory effect of local anesthetics on the Ca^{++}-dependent cellular functions is mediated by the role played by calmodulin. The present results showing that the ratio of potency in inhibiting the myosin light-chain kinase correlates with the hydrophobicity expressed by the oil solubility (19) support this concept. Similar results were reported by Tanaka and Hidaka (25). The relatively benign effect of lidocaine on hemodynamics may be related to the relatively hydrophilic property of lidocaine.

The present results do not mean that calcium administration has no therapeutic value in the presence of local anesthetic-induced cardiovascular toxicity. The action of calcium on the contractile process in vascular muscle is multifaceted, and the mechanism of contraction of smooth muscles is only starting to be revealed. Antagonisms between cationic local anesthetics and calcium ion can be expected at various steps.

The concentrations of cationic local anesthetics near the surfaces of phospholipids with single negative charge can be estimated using the above equation. The area occupied per lipid molecule in bilayer membranes is about 55 to 60 $Å^2$. When $T = 310$ K, $C = 0.15$ M, $f = 60$ $Å^2$, and assuming that σ is similar to water, the concentration of the charged forms near the membrane surface is about 150 times higher than in the bulk solution. The value varies according to the charge density, the permittivity of the binding site, electrolytes, etc. This condensing effect appears to be a contributing factor to the anesthetic efficacy at the physiological pH where local anesthetics exist mainly in the charged form.

Appendix

Membrane Surface Concentration of Charged Local Anesthetics

The surface concentration of the cationic anesthetics is estimated from the bulk pH and the surface charge density according to the Gouy-Chapman theory. In univalent electrolyte solutions, the surface concentration of charged local anesthetics is written in SI units:

$$[LH^+]_0 = [LH^+]_\infty \frac{\sigma^2}{2000 \; \epsilon\epsilon_0 CRTf^2}$$

where $[LH^+]$ is the charged local anesthetics, subscripts 0 and ∞ signify the concentrations at the membrane surface (electrical diffuse double layer) and bulk, respectively, σ is the surface charge density, ϵ is the relative electrical permittivity of the solution, ϵ_0 is the electrical permittivity of vacuum, C is the counterion concentration in M, R is the gas constant, T is the absolute temperature, and f is the area per charged site.

References

1. Somlyo AP, Somlyo AV. Vascular smooth muscle. Pharmacol Rev 1968;20:197–272.
2. Bianchi CP, Bolton TC. Action of local anesthetics on coupling systems in muscle. J Pharmacol Exp Ther 1967;157:388–405.
3. Feinstein MB, Paimre M. Pharmacological action of local anesthetics on excitation-contraction coupling in striated and smooth muscle. Fed Proc 1969;28:1643–48.
4. Endo M. Calcium release from the sarcoplasmic reticulum. Physiol Rev 1977;57:71–108.
5. Bianchi CP, Bolton TC. Action of local anesthetics on coupling system in muscle. J Pharmacol Exp Ther 1967;157:388–405.
6. Wilcox WD, Fuchs F. The effect of some local anesthetic compounds on sarcotubular calcium transport. Biochim Biophys Acta 1969;180:210–2.
7. Madeira VMC, Carvalho AP. Interaction of cations and local anesthetics with isolated sarcolemma. Biochim Biophys Acta 1972;266:670–83.
8. Katz AM, Repke DI, Corkedale S, Schwarz J. Effects of local anesthetics on calcium transport by canine cardiac microsomes (fragmented sarcoplasmic reticulum). Cardiovasc Res 1975; 9:764–9.
9. Escudero B, Gutiérrez-Merino C. Effects of local anesthetics on the passive permeability of sarcoplasmic reticulum vesicles to Ca^{++} and Mg^{++}. Biochim Biophys Acta 1987;902:374–84.
10. Stephenson DG, Wendt IR. Effects of procaine on calcium accumulation by the sarcoplasmic reticulum of mechanically disrupted rat cardiac muscle. J Physiol 1986;373:195–207.
11. Small JV, Sobieszek A. The contractile apparatus of smooth muscle. Int Rev Cytol 1980;64:241–306.
12. Hartshorne DJ, Siemankowski RF. Regulation of smooth muscle actomyosin. Ann Rev Physiol 1981;43:519–30.
13. Ebashi S, Nonomura Y, Hirata H. Mode of calcium binding to smooth muscle contractile system. In: Kakiuchi H, Hidaka H, Means AR, eds. Calcium and Intracellular Ca^{2+} Receptors. New York: Plenum, 1982:189–98.
14. Kamm KE, Stull JT. The function of myosin and myosin light chain kinase phosphorylation in smooth muscle. Ann Rev Pharmacol Toxicol 1985;25:593–620.
15. Dabrowska R, Hinkins S, Walsh MP, Hartshorne DJ. The binding of smooth muscle myosin light chain kinase to actin. Biochem Biophys Res Commun 1982;107:1524–31.
16. Bradford M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Analyt Biochem 1976;72:248–54.

17. Adelstein RS, Klee CB. Purification and characterization of smooth muscle myosin light chain kinase. J Biol Chem 1981; 256:7501-9.

18. Chacko S, Rosenfeld A. Regulation of actin-activated ATP hydrolysis by arterial myosin. Proc Natl Acad Sci USA 1982; 79:292-6.

19. Savarese JJ, Covino BG. Basic and clinical pharmacology of local anesthetic drugs. In: Miller RD, ed. Anesthesia vol 2. 2nd ed. New York: Churchill Livingstone, 1986:985-1013.

20. Åberg G, Wahlström. Mechanical and electrophysiological effects of some local anaesthetic agents and their isomers on the rat portal vein. Acta Pharmacol Toxicol 1972;31:225-66.

21. Nishimura N, Morioka T, Sato S, Kuba T. Effects of local anesthetic agents on the peripheral vascular system. Anesth Analg 1965;44:135-9.

22. Johns RA, DiFazio CA, Longnecker DE. Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. Anesthesiology 1985;62:141-44.

23. Johns RA, Seyde WC, DiFazio CA, Longnecker DE. Dose-dependent effects of bupivacaine on rat muscle arterioles. Anesthesiology 1986;65:186-91.

24. Lynch C III. Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 1986; 65:551-9.

25. Tanaka T, Hidaka H. Interaction of local anesthetics with calmodulin. Biochem Biophys Res Commun 1981;101:447-53.

26. Volpi M, Sha'afi RI, Feinstein MB. Antagonism of calmodulin by local anesthetics inhibition of calmodulin stimulated calcium transport of erythrocyte inside-out membrane vesicles. Mol Pharmacol 1981;20:363-70.

27. Volpi M, Sha'afi RI, Epstein PM, Andrenyak DM, Feinstein MB. Local anesthetics mepacrine and propranolol are antagonists of calmodulin. Proc Natl Acad Sci USA 1981;78:795-9.

28. Muto Y, Kudo S, Nozawa Y. Effects of local anesthetics on calmodulin dependent guanylate cyclase EC-4.6.1.2 in the plasma membrane of tetrahymena-pyriformis. Biochem Pharmacol 1983;32:3559-64.

29. Hirata M, Mikawa T, Nonomura Y, Ebashi S. Ca^{++} regulation in vascular smooth muscle. J Biochem 1977;82:1793-6.

Special Article

Standardization of the Caffeine Halothane Muscle Contracture Test

Marilyn Green Larach, MD, FAAP* for the North American Malignant Hyperthermia Group*,†

Key Words: HYPERTHERMIA, MALIGNANT.

On November 4–6, 1987, 47 representatives from 24 North American malignant hyperthermia (MH) testing centers met in Lake Bluff, Illinois, to discuss development of a standardized protocol for skeletal muscle contracture testing using caffeine and halothane. The caffeine halothane contracture test is a screening test that requires use of fresh muscle and is used in the diagnosis of MH susceptibility. A standardized protocol for caffeine halothane contracture testing has been previously established in Europe by the European Malignant Hyperpyrexia Group (see p. 515). The European protocol differs in several minor aspects from the North American protocol, with the primary difference involving exposure of muscle to 2% rather than 3% halothane. This article represents the consensus achieved by the 47 representatives who shall hereafter be referred to as the North American MH Group who convened under the sponsorship of the Malignant Hyperthermia Association of the United States and the Malignant Hyperthermia Association. The recommended protocol of the North

American MH Group for caffeine halothane contracture testing follows.

The Biopsy: Site, Anesthetic, and Surgical Management

The order of preferred sites for muscle biopsy shall be: 1) the vastus group; 2) the rectus abdominus; and 3) other muscle groups under special circumstances. When sufficient data are collected on control and malignant hyperthermia susceptible patients, the caffeine halothane contracture responses from the above sites shall be compared.

Whenever possible, a period of at least 2 to 3 months should elapse between diagnostic muscle biopsy and a patient's experience of either: fulminant MH or significant rhabdomyolysis (as determined by clinical history or laboratory documentation of a creatine kinase >10,000 IU/L). For the results of a MH diagnostic muscle biopsy to be considered valid after recent fulminant MH or significant rhabdomyolysis, a histologic examination must also be performed that documents no significant evidence of muscle destruction.

In addition, histological and histochemical examination of muscle obtained from each patient who is undergoing caffeine halothane contracture testing is strongly recommended.

Patients undergoing diagnostic MH muscle biopsy may receive any nontriggering anesthetic agent as long as the anesthetic is not preceded by dantrolene administration. A standard anesthetic regimen is encouraged to avoid possible pharmacologic effects.

Careful surgical technique must be used to successfully obtain viable muscle for biopsy testing. Care

should be taken to ensure that the specimen is not stretched and that the portion of the specimen that will undergo testing is not handled. When excised, the specimen may be either clamped or unclamped. The muscle specimen should be transported at room temperature in a Krebs-Ringer solution that may or may not be carbogenated. All testing on the muscle specimen should be completed within 5 hr of muscle excision.

The Fascicle: Dissection, Dimensions, Bath, Solutions, Twitch Parameters, and Stimulation

Dissection

The muscle should be dissected sharply (with scissors) and in the direction of the fibers. During dissection and mounting, the belly of the muscle should not be handled. The muscle fascicle should be either tied with black silk suture or clamped completely across each end. Before testing, the muscle fascicle should be examined with either a magnifying glass or a microscope to eliminate all fascicles with nicks. Before their use, extra specimens should be kept at room temperature in carbogenated Krebs-Ringer solution.

Dimensions

At the end of the contracture test, while the specimen is still mounted on the frame between the silk ties or clamps, the bath should be drained and the dimensions of the muscle fascicle should be measured. The fascicle should be 1-2 cm in length; usual widths will be 0.1-0.5 cm. The weight of the muscle should be determined after cutting the muscle ends off just within the silk ties (or clamp) and blotting the muscle dry on filter paper. The average cross-sectional area (CSA) of the muscle fascicle should be calculated from the following formula:

$$\text{CSA } [\text{cm}^2] = \frac{\text{weight } [g]}{1.06 \ [\frac{g}{cm^3}] \cdot \text{length } [\text{cm}]}$$

Bath

There should be at least two glass chambers that are periodically washed with acid or detergent and extensively rinsed before their use. As long as the

concentrations of halothane present in solution are periodically checked, the size of the glass chambers may vary. All tubing used in the carbogen/carbogen plus halothane lines shall be made of Teflon to decrease the amount of anesthetic adsorption unless the anesthetic (carbogen plus halothane) line is totally separate from the carbogen line. All muscle biopsy testing should take place in a hood so that anesthetic gases may be scavenged. Gloves should be worn when one is coming into contact with potentially infectious material.

Solutions

A human Krebs-Ringer solution shall be used after it is buffered with carbogen (95% O_2/5% CO_2). The temperature of all testing solutions shall be 37°C. After carbogen has been added to the solution, the pH of the solution shall be: 7.4 ± 0.1 at 37°C. The pH of the solution should be checked each day that bulk buffer is mixed.

When caffeine solutions are prepared, the free base caffeine should be thoroughly dissolved in a carbogenated human Krebs-Ringer solution that is maintained at a pH of 7.4 ± 0.1 and a temperature of 37°C.

To ensure minimal contamination of the tissue bath by halothane, the concentration of halothane present in the bath when the halothane vaporizers are off shall be checked periodically. On each testing day, the halothane gas concentration should be measured immediately before its point of entrance into the bath solution. The halothane concentration within the liquid phase of the bath solution should be correlated at regular intervals with the halothane concentration within the gas phase.

Twitch Parameters

Linear calibration of the force transducer with a known gram weight should be completed and shown on the trace record before muscle biopsy testing. After transducer calibration, the muscle fascicle should be placed in a Krebs-Ringer solution and equilibrated for a period of 15-60 min until stable twitch height and twitch baselines are achieved.

Equilibration should take place at either a starting tension of 1-2 g or at an optimal length that is determined by first reversing polarity to obtain maximal response, then increasing the voltage to supramaximal twitch tension and finally, increasing the length to achieve absolute twitch tension.

Stimulation

Whenever a drug response is being assayed, the muscle should be stimulated at 0.1–0.2 Hz (every 5–10 sec) with a pulse duration of 1–5 msec to confirm muscle viability.

The stimulator should produce sufficient voltage and current to allow for the attainment of supramaximal voltage (110% of the voltage that produces maximal twitch) in all tested fibers.

The ideal stimulating electrode is a platinum plate or platinum prong. Platinum prongs should be 0.5–1.0 mm in diameter (smaller sizes require muscle damaging voltage).

Contracture Testing: Halothane, Caffeine, Joint Halothane, and Caffeine Assay

General Principles

For diagnostic purposes, each diagnostic test should be performed on a fresh muscle strip i.e. each muscle strip should be used for only one test. Whenever possible, a minimum of three muscle strips should be tested for each of the separate drugs assayed. Good twitch viability in each specimen should be demonstrated before its testing. Required tests include exposure of muscle strips to 3% (v/v) halothane alone and to incremental caffeine concentrations alone. Optional tests include exposure of muscle strips to a combination of both 1% halothane and incremental caffeine concentrations, and to 2% halothane alone.

3% Halothane-Required Testing (Amplitude of 3% Halothane Induced Contraction)

The following conditions should prevail before muscle testing begins. The vaporizer should be functional and should be observed for the development of back pressure that should be eliminated before testing.

Muscle strips should be exposed to 3% halothane (or a 21 mm Hg partial pressure of halothane measured at sea level and saturated with water vapor at 37°C) at the point immediately before entry into the bath solution. The range of acceptable halothane levels is 2.7%–3.3% (19–24 mm Hg partial pressure). The duration of halothane exposure shall be 10 min.

The contracture response to halothane should be measured. By analogy with most clinical laboratory tests, the specific upper limit of normal contracture value for each lab shall be determined by each lab after testing at least 30 normal control patients.

Caffeine-Required Testing (Caffeine Specific Concentration)

The caffeine concentrations used in the testing bath shall be: 0.5 mM, 1 mM, 2 mM, 4 mM, (8 mM if the response at 4 mM is <1 g), and 32 mM. These concentrations can be achieved either by incremental drug addition or by fully replacing the bath contents. The muscle strip should be exposed to each concentration except 32 mM for at least 4 min or until a contracture plateau is achieved (whichever is longer). The muscle strip should be exposed to a 32 mM caffeine solution for at least 10 min or until a double peak is observed, whichever is longer.

The contracture response to each dose of caffeine shall be measured. The caffeine specific concentration is defined as the caffeine concentration required to produce a net increase above the baseline of 1 g. The caffeine specific concentration is estimated by graphing grams contracture on the y axis and log concentration of caffeine on the x axis.

Baseline tension should be set using the optimal length of the fiber with the maximum tension equal to the response at 32 mM caffeine. Percent of maximal tension is calculated with the following formula: Percent maximal tension = {tension at x mM caffeine − control tension without caffeine} × 100 ÷ total tension at 32 mM caffeine − control tension without caffeine.

Joint Halothane and Caffeine Assay-Optional Testing (Halothane-Caffeine Specific Concentrations)

Muscle strips should be exposed first to 1% halothane for 10 min. After this halothane exposure, caffeine at 0.25 mM, 0.5 mM, 1 mM, 2 mM, 4 mM, and 32 mM should be added incrementally to the bath solution. Except for the 32 mM caffeine exposure of 10 min, each caffeine exposure should be maintained for 4 min or until a contracture plateau is achieved (whichever is longer).

This is an optional test. Not all laboratories consider it valid.

2% Halothane-Optional Testing (Amplitude of 2% Halothane-Induced Contractions)

For this optional test, the testing conditions shall be the same as those for the 3% halothane test except that the muscle shall be exposed to a 2% halothane concentration (as measured in the gas phase). Laboratories are encouraged to perform this test whenever possible.

Diagnosis of MH Susceptibility

Because values for normals vary among labs currently in existence, the following general *guidelines* have been developed. These guidelines are subject to modification by the North American MH group when further data on normal controls and clinically unequivocal MH susceptible patients are reported and analyzed.

For purposes of clinical diagnosis, a patient shall be considered to be MH susceptible even if only **one** of his viable muscle strips demonstrates an abnormal contracture response after exposure to either 3% halothane alone, caffeine alone, or for those labs performing this test, the joint halothane and caffeine assay.

An abnormal contracture response or a positive malignant hyperthermia muscle biopsy is defined as follows.

- A positive halothane contracture test is defined as a >0.2-0.7 g contracture after exposure to 3% halothane for 10 min. The exact value of this range of abnormal shall be determined by each testing laboratory after the evaluation of at least 30 normal control muscle biopsies.
- A positive caffeine contracture test is defined as the observation of either: 1) the development of ≥0.2 g tension at 2 mM caffeine or 2) a caffeine specific concentration (CSC) at <4 mM caffeine or 3) the percent of maximal tension is >7% change above the baseline at 2 mM caffeine.
- A positive joint halothane and caffeine contracture assay is defined as the development of a 1 g contracture after exposure to a concentration of 1 mM or less caffeine in the presence of 1% halothane. These are suggested values and must be modified by each lab.

Future Biopsy Research Areas

Areas of future research and data collection should include the following.

- A comparison of 2% halothane contracture response with 3% halothane contracture response in known MH susceptible patients and normal control patients.
- Determination of the usefulness of the joint halothane and caffeine assay for predicting MH susceptibility. Evaluation of the significance of the "K" phenotype responder.
- Evaluation of the relationship between MH susceptibility and observed spontaneous muscle

contracture (contractures developing just after placement of muscle strips in the bath).
- Analysis of the outcomes of triggering anesthetic administration to biopsy proven MH nonsusceptible (negative caffeine halothane contracture test) patients.
- Validation of each muscle biopsy center's contracture testing technique through their biopsy of normal control patients and patients who have experienced fulminant MH.
- Exploration of the utility of ryanodine contracture testing and hypoxia testing for the determination of MH susceptibility.

Biopsy Indications

While the caffeine halothane contracture test is being standardized, it is recommended that all patients with a clinical history of unequivocal MH have biopsy performed. Whenever possible, every MH proband should have biopsy performed. All patients who have undergone a clinical episode that is possibly MH (including the experience of trismus that led to difficulty in opening the mouth) should have biopsy performed.

Before undergoing muscle biopsy, children should have a lean body mass of ≥20 kg. Only one parent of a proband need be tested if the first parent is found to be susceptible unless there are exceptional circumstances. The second parent should undergo testing if the first parent is found to be nonsusceptible to document sporadic mutations as well as to test the diagnostic capabilities of each laboratory.

It is imperative that dantrolene not be taken before biopsy. In addition, calcium channel blocking agents are best avoided whenever possible.

Recommendations for Muscle Biopsy Report

A physician should always serve as the link between the patient and the muscle biopsy testing center. A letter should be sent to the patient that summarizes indications for biopsy, prior history of any adverse anesthetic reaction, tests performed for MH evaluation (i.e. caffeine, halothane, joint halothane and caffeine assay muscle histology, muscle histochemistry), testing results, evaluation of the reliability of these tests for this individual patient's diagnosis, and recommendations for future anesthetic management. The patient should also be advised to wear a Medic-Alert bracelet and be given the office telephone

numbers of the patient groups, MHA and/or MHAUS.

The patient's referring physician should receive a copy of the letter that is sent to the patient as well as the official laboratory evaluation form.

Methods for the Establishment of New Diagnostic Muscle Centers

It is recommended that new labs first test their experimental setup with animals. Diagnostic muscle biopsies should not be performed until a minimum of 10 normal control patients are tested and found to be normal by the new laboratory. It is recommended that all diagnostic laboratories test 30 normal control patients as soon as possible to validate the new standardized testing protocols. Results of control patient testing shall be reported to the NAMH Registry.

North American Malignant Hyperthermia Registry

In order to permit the accumulation of comparative data, the North American Malignant Hyperthermia Group proposed and accepted a resolution for the establishment of the North American Malignant Hyperthermia Registry ("Registry"). All participating MH testing centers will report diagnostic and control muscle biopsy data to the Registry.

The North American Malignant Hyperthermia Registry, Inc. has been established through the cooperation of the American Society of Anesthesiologists, the North American Malignant Hyperthermia Group, the Malignant Hyperthermia Association of the United States, and the Malignant Hyperthermia Association, to provide database, statistical, and epidemiologic support for the malignant hyperthermia community. The Registry is located at the Department of Anesthesia of the Pennsylvania State University College of Medicine.

The Registry will analyze submitted data to further validate the North American protocol for caffeine halothane contracture testing. Results of Registry data analysis will be presented to the North American MH Group when they reconvene in November 1989 at Lake Bluff, Illinois, allowing for amendation of the North American caffeine halothane contracture test protocol. Therefore, it is anticipated that the standards contained in this report will undergo a process of evolution, as more information concerning the specificity and sensitivity of the test is obtained.

The North American Malignant Hyperthermia Group
Active Biopsy Centers: Hahnemann University (Jeffrey E. Fletcher PhD; Henry Rosenberg MD), Loyola University (Silas N. Glisson PhD; Philip Kober PhD; Jeejy R. Kalathiveetil MD; Kamlesh Shah MD), Mayo Clinic (James P. Conterato MD; Denise J. Wedel MD), Ottawa Civic Hospital (Gregory Allen MD; Charles Cattran MD, FRCPC; Kevin Nolan MD, FRCPC), Toronto General Hospital (Beverly A. Britt MD; Wanda Frodis BSc), Uniformed Services University of the Health Sciences (William Freas PhD; Jean A. Greuter MD; Janice E. Horahov MS; Sheila M. Muldoon MD [not present]), University of Calgary (A. Keith W. Brownell MD, FRCPC; Rein T. Paasuke MD, FRCPC), University of California at Davis (Gerald A. Gronert MD), University of California at Los Angeles (Martin E. Mann MD; Imad H. Rasool MD), University of Florida (Richard F. Kaplan MD) University of Iowa (Lloyd R. Davies BS; Martin D. Sokoll MD), University of Manitoba (Deepak D. Bose MD, PhD; Leena R. Patel MD, FRCPC), University of Massachusetts (Michael W. Perkins BS; Barbara E. Waud MD), University of Nebraska (Dennis F. Landers MD, PhD), University of Texas Health Science Center [Houston] (Basil C. Leiman MD; Thomas E. Nelson PhD) University of Washington (Shenton Oh MB, FFARCS; Judy Y. Su PhD).

Centers Preparing for Biopsies: Cleveland Clinic (Gisela Bunge BS; Glenn E. DeBoer MD), Mary Imogene Basset Hospital (Carol J. Bedworth AAS; Robert Quarmby MD), State University of New York (Michael G. Adragna MD), University of Pittsburgh (Marshall S. Millman MD, PhD; Peter Waterman MD), University of Saskatchewan (Brian R. MacIntosh PhD; F. Barrie Reynolds MD, FRCPC), University of Texas Medical Branch (Sharon Nelson PhD), University of Wisconsin (John F. Kreul MD; Robert L. Sufit MD; James A. Will DVM, PhD), Washington University (Mehernoor F. Watcha MD, DCh).

The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anesth 1984;56:1267-9.

References (Suggested Reading)

Britt BA. Muscle assessment of malignant hyperthermia susceptible patients. In: Britt BA, ed. Malignant Hyperthermia. Boston: Martinus Nijhoff, 1987:193-267.

Fletcher JE, Rosenberg H. Laboratory methods for malignant hyperthermia diagnosis. In: Williams CH, ed. Experimental Malignant Hyperthermia. New York: Springer-Verlag, 1988:121-40.

Gronert GA. Contracture responses and energy stores in quadriceps muscle from humans age 7-82 years. Hum Biol 1980;52:43-51.

The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. Br J Anaesth. 1984;56:1267-9.

Clinical Reports

Accidental Subarachnoid Injection of Pancuronium

Vito A. Peduto, MD, Paolo Gungui, MD, Maria R. Di Martino, MD, and
Marina Napoleone, MD

Epidural or subarachnoid analgesia is a common and well-established method for surgical anesthesia, postoperative and obstetric analgesia, and control of chronic pain. However, the increasing application of epidural and subdural local anesthetic and/or narcotic administration may be accompanied by the hazard that other drugs may be accidentally administered into the epidural or subarachnoid space.

The present case report describes a patient who developed subjective weakness and a generalized muscle hypotonia after inadvertent subarachnoidal injection of pancuronium bromide.

Case Report

A 35-year-old woman weighing 65 kg was scheduled to have a cesarean section for fetal distress during labor. Her medical history and physical examination revealed no abnormality and it was decided to give her a spinal anesthetic. Shortly before the anesthetic procedure 0.5 mg of atropine was given IM as premedication. She was taken to the operating room. An IV infusion was started, monitoring devices were applied, and a lumbar puncture was performed, with the patient in the left lateral position. A 7.5-cm 22-gauge spinal needle was placed in the subarachnoid space at the L2–3 interspace using a median approach. Its position was confirmed by the appearance of cerebrospinal fluid coming from the needle.

When the anesthetist performing the block needed to fill the syringe being used, his assistant mistakenly passed him an open ampule containing 2 mL (4 mg) of pancuronium bromide (Pavulon. Organon, Oss, Holland) instead of a 2-mL vial of hyperbaric 1% bupivacaine solution. The contents of the ampule were aspirated into the syringe and then injected into the subarachnoid space.

At this stage the patient did not complain of any pain or discomfort. She was then placed in the supine position with a pillow under her shoulders and head. Usually, this technique gives a level of analgesia up to the T-8 dermatome. When assessment of the level of analgesia to pinprick was made 5 min later, it was apparent that there was no analgesia. The patient was therefore managed as a case of "failed spinal," and another spinal anesthesia was therefore carried out using the same technique. This time there was no error in making the injection. Satisfactory analgesia to pinprick up to the T-9 dermatome was achieved with subarachnoid injection of 2 mL of hyperbaric 1% bupivacaine solution, and surgery was started.

Approximately 15 min after the inadvertent injection of pancuronium bromide, the patient showed a progressive and generalized muscle hypotonia, with a subjective feeling and inability to breathe adequately. Her ability to open and close her eyes, to protrude her tongue and to swallow, as well as her handgrip strength and head lift were moderately affected. At this time, she became slightly cyanotic and agitated, without evidence of cephalad progression of analgesia to pinprick beyond the T-9 dermatome.

Oxygen was administered by mask and assisted ventilation (without intubation) was started. The fact that 4 mg of pancuronium bromide had been administered instead of hyperbaric 1% bupivacaine solution came to light at this point when the empty ampule

was discovered. Confirmatory evidence for a partial neuromuscular blockade was supplied by spirometric evaluation of tidal volume and inspiratory force. At this time electromyographic monitoring of neuromuscular function was not available.

It was then decided to reverse the neuromuscular blockade promptly with injection of neostigmine 2.5 mg and atropine 1.0 mg IV. Within minutes hypoventilation disappeared. At 15 min after neuromuscular blockade reversal, no acid–base abnormalities were present; at the same blood pressure was 110/79 mm Hg, pulse rate 84 beats/min, respiratory rate 20 breaths/min, and temperature 36.8°C.

The operation was completed in 55 min. Apgar scores of the female infant were 6 at 1 min, and 9 at 5 min. About 1 hr after surgery the patient started to move her legs and cutaneous sensation had returned to normal. The patient's first postoperative day was uneventful. In the second postoperative day a neurological examination revealed no sensory, motor, or reflex changes. Clinical examination 3 months later again revealed no sequelae.

Discussion

Accidental injection of the wrong drug into epidural or subdural space has previously been reported (1–8). The case described here is the latest in an unfortunately long series of such misadventures in which the user failed to identify correctly the contents of ampules and syringes and the drug to be injected.

Although the patient recovered with no neurologic sequelae, there is clinical and experimental evidence that convulsions and neuronal death result when quaternary ammonium neuromuscular blocking drugs such as gallamine or d-tubocurarine are directly applied to the brain or accidentally injected into lumbar CSF (9–12).

Since in our patient only generalized muscle hypotonia developed, with no evidence of neurologic dysfunction outside the area made anesthetic by the subsequent intrathecal injection of bupivacaine, the pancuronium probably remained in the lower part of dural sac without significant spread from lumbar spinal fluid to brain. This is not in keeping with the well-known propensity for pregnant women at term to develop higher levels of spinal anesthesia than those of nonpregnant women because of higher rostral spread of spinal local anesthetic solutions. It is

possible that hyperbaric 1% bupivacaine solution, injected a few minutes after pancuronium, might have helped restrict diffusion of the pancuronium out of the lumbar area. In any event, the pancuronium, a highly ionized and hydrophilic drug, moves slowly out the cerebrospinal fluid (CSF) with uptake into the systemic circulation. The result, as in our patient, can be a plasma concentration of pancuronium too low to produce complete neuromuscular blockade but enough to impair normal muscle function.

The potential for administering the wrong drug is always present in anesthetic practice. This case highlights yet again the danger in having other drugs drawn up and at hand when regional, spinal, or epidural techniques are being employed. This case also demonstrates that although accidental subarachnoid injection of pancuronium was, at least in this instance, devoid of neurologic sequelae, there is enough absorption of pancuronium from the CSF into the systemic circulation to depress but not completely block normal muscle function.

References

1. Forestner JE, Raj PP. Inadvertent epidural injection of thiopental: a case report. Anesth Analg 1975;54:406–7.

2. Aghdami A, Keenan RL, Boyan CP. Inadvertent caudal injection of thiopental: a case report. Anesthesiol Rev 1979;6:38–9.

3. Brahams D. Record award of personal injuries sustained as a result of negligent administration of epidural anaesthetic. Lancet 1982;1:159.

4. Brownridge P. More on epidural thiopentone. Anesth Intensive Care 1984;12:270–1.

5. Cay DL. Accidental epidural thiopentone. Anaesth Intensive Care 1984;12:61–3.

6. Shanker KB, Palkar NV, Nishkala R. Paraplegia following epidural potassium chloride. Anaesthesia 1985;40:45–7.

7. Lin D, Becker K, Shapiro HM. Neurologic changes following epidural injection of potassium chloride and diazepam: a case report with laboratory correlations. Anesthesiology 1986;65:210–2.

8. Dror A, Henriksen E. Accidental epidural magnesium sulfate injection. Anesth Analg 1987;66:1020–1.

9. Mesry S, Baradaran J. Accidental intrathecal injection of gallamine triethiodide. Anaesthesia 1974;29:301–4.

10. Goonewardene TW, Sentheshanmuganathan S, Kamalathan S, Kanagasundereram R. Accidental subarachnoid injection of gallamine: a case report. Br J Anaesth 1975;47:889–93.

11. Salama S, Wright S. Action of d-tubocurarine chloride on the CNS of the cat. Br J Pharmacol 1950;5:49–52.

12. Dasheiff RM. d-Tubocurarine causes neuronal death when injected directly into rat brain. Exp Neurol 1985;89:172–88.

Increased Requirements for Continuously Infused Vecuronium in Critically Ill Patients

Douglas B. Coursin, MD, George Klasek, RPh, and Susan L. Goelzer, MD

Critically ill patients with respiratory failure who require positive pressure ventilation are routinely given sedative agents and narcotic analgesics. If gas exchange is still inadequate or lung compliance decreases significantly, muscle relaxants are frequently administered. The newer intermediate acting nondepolarizing muscle relaxants, vecuronium and atracurium, are often administered by continuous infusion. Minimal information is available in the literature on the use of long-term vecuronium infusions in patients with multiple organ failure in the intensive care unit. The initial reports in these patients given vecuronium infusions indicate that at a fixed dose, even one below that suggested for surgical use (i.e. 0.07–0.10 $mg \cdot kg^{-1} \cdot hr^{-1}$), gradually increasing block may develop (1).

We have used vecuronium infusions on many occasions in our intensive care unit (ICU) starting with a loading dose of 0.1 mg/kg body weight via a central venous catheter followed, within 30 min, by an infusion at the rate of 0.08–0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$ (2). The rate of administration is adjusted to permit controlled ventilation without patient initiated attempts at spontaneous ventilation. Nerve stimulators placed over the ulnar nerve are used, as needed, to follow responses to train of four and tetanic stimuli to avoid excessive drug administration. Nerve stimulators are also used to assess the degree of neuromuscular recovery after discontinuation of a prolonged infusion of relaxant. Patients are also treated with infusions of sedative/narcotics such as midazolam or morphine, as required, to maintain amnesia, comfort, and hemodynamic stability.

We report two patients who received prolonged infusions with vecuronium and, as opposed to previous reports, required significant increases in dosage, over time, to maintain adequate relaxation.

Case 1

A 38-year-old white female patient, weighing 48 kg, was transferred to our institution 2 weeks after the onset of a viral syndrome with nausea, vomiting, malaise, fever, and nonproductive cough. She had developed severe adult respiratory distress syndrome (ARDS) with associated barotrauma. Initial evaluation, including bronchoalveolar lavage and open lung biopsy, revealed only diffuse alveolar damage with hyaline membranes and focal fibrosis of a nonspecific etiology. She was transferred to the ICU for potential extracorporeal membrane oxygenation (ECMO) therapy and chronic ventilatory support. On admission, she was receiving diazepam and morphine for sedation and analgesia, respectively. She had peak airway pressures of 70 cm H_2O and required a minute ventilation of 25 L to maintain a $Paco_2$ of 70–80 mm Hg with a partially compensated respiratory acidosis. Vital signs were stable except for brief intermittent severe hypotensive episodes related to air trapping with auto-PEEP, asynchronous ventilation, or spontaneous pneumothorax. The patient was electively paralyzed with vecuronium 0.1 mg/kg and started on a vecuronium infusion of 0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$ (5 mg/hr). This was done to stop the patient from triggering the ventilator, to optimize gas exchange, and to minimize the development of further barotrauma while different modes of high frequency ventilation were utilized. Over the course of 8 weeks, the requirements of the patient for vecuronium increased approximately 6-fold (32 mg/hr) to maintain adequate relaxation for controlled ventilation. The degree of muscle relaxation was intermittently checked with a

nerve stimulator. At all times, there was at least one twitch present in the train of four. This progressive relative resistance to vecuronium occurred despite improvement of $Paco_2$, stabilization of acid-base balance, maintenance of normothermia, aggressive nutritional support, and treatment with aminoglycoside antibiotics and vancomycin of *E. coli* and *Staph epidermidis* sepsis. After a prolonged and stormy course, the patient had the vecuronium infusion discontinued with prompt recovery of neuromuscular function, as evidenced by return of the train of four on the neuromuscular monitor within 1 hr, eye opening, spontaneous respiration, and movement of all four extremities within 12 hr. Within 24 hr she was able to follow verbal commands and communicate appropriately although she remained on continuous infusions of midazolam (40 mg/hr) and morphine (10 mg/hr). As her sedation was tapered, she was eventually weaned from mechanical ventilation and was discharged from the ICU after 14 weeks. She was discharged from the hospital after an additional 4 weeks of rehabilitation and is now at home using occasional low flow supplemental oxygen.

Case 2

A 21-year-old white female patient, weighing 46 kg, was transferred to our hospital 2 weeks after a motor vehicle accident in which she sustained pubic symphysis fractures, maxillary fractures, blunt abdominal trauma with a ruptured spleen, liver lacerations, renal hematoma and an abruptio placenta with a 38 week old stillborn infant, and hemorrhagic shock. She underwent initial exploratory laparotomy with splenectomy, repair of liver lacerations and multiple serosal tears, and required massive transfusion. A hysterotomy was also performed with evacuation of the fetus and placenta. The postoperative course was complicated by disseminated intravascular coagulation, sepsis, right retroperitoneal hematoma, and ARDS. A second laparotomy was performed to drain the retroperitoneal hematoma. On transfer to our ICU, the patient was supported with controlled mechanical ventilation and had two chest tubes in place for treatment of bilateral pneumothoraces. Both chest tubes had large air leaks and ventilation was marginal with a Pao_2 of 51 mm Hg and $Paco_2$ of 58 mm Hg. Chest x-ray revealed bilateral diffuse alveolar infiltrates consistent with ARDS as well as multiple bilateral pneumothoraces. Over the first 24 hr after admission, the patient developed progressive barotrauma and hypoxemia despite use of various modes of high frequency ventilation and maneuvers to de-

crease peak airway pressures and thereby limit air leaks. The intractable hypoxemia and inadequate ventilation precipitated the initiation of ECMO combined with low frequency ventilation (3). Shortly after her transfer to our unit, the patient was sedated with a continuous infusion of midazolam and electively paralyzed with 0.1 mg/kg of vecuronium followed by an infusion of $0.1~mg \cdot kg^{-1} \cdot hr^{-1}$ of vecuronium. During the following 12 weeks, the patient required increasing doses of vecuronium, which peaked at 25 mg/hr to maintain controlled ventilation without spontaneous respiratory efforts. After a 1 week course of ECMO, the patient had multiple septic episodes and marked hepatic dysfunction developed over the ensuing 2 months. She continued to require high inspired concentrations of oxygen and a high minute ventilation to maintain even borderline oxygenation. She was also given blood component therapy as well as tobramycin, ticarcillin, azthreonem, vancomycin, and ciprofloxacin for *Pseudomonas* pneumonia and sepsis and *Staph epidermidis* septicemia. She also received total parenteral nutrition and routine aggressive care. The vecuronium was discontinued after 12 weeks with recovery of neuromuscular function within 12 hr, sedation was tapered, and the patient was slowly weaned from the ventilator. She underwent rehabilitation and is now home using low flow oxygen therapy intermittently.

Discussion

The cases reported describe our recent experience with long-term infusions of vecuronium in two critically ill patients who suffered from severe adult respiratory distress syndrome and intermittent sepsis. There are few if any data available in the literature describing similar clinical responses. This may reflect the relative lack of experience with vecuronium for such prolonged periods in critically ill patients or lack of recognition of an increase in dose requirements over long-term infusions.

The pharmacokinetics and pharmacodynamics of vecuronium have been well characterized in healthy patients as well as in individuals with renal or hepatic dysfunction (4-7). In these studies, short-term bolus injections or infusions of vecuronium were used. Vecuronium is poorly protein bound and has limited lipid solubility (8). Therefore, alterations in protein binding as well as changes in body fat that occur with malnutrition or during a highly catabolic state should have little effect on drug requirements. Although vecuronium metabolites possess pharmacologic effects, vecuronium and other drugs have not been

shown to induce their metabolism (9,10). Vecuronium, however, has been shown to have a prolonged effect in patients with renal insufficiency (7). It has been our clinical experience that despite the potential for prolonged effects, vecuronium is safe to administer to the critically ill.

Smith et al. (1) studied seven intensive care unit patients with renal and respiratory failure while receiving infusions of vecuronium for 6.75 to 30 hr (1). They found a prolonged recovery phase of 6-37 hr after infusions of vecuronium that lasted only several hours. In addition, they found that during this relatively short infusion period, full neuromuscular blockade may not be present during the first few hours but that a gradually increasing block ensued, despite a constant rate of vecuronium infusion. Prolonged recovery from vecuronium induced neuromuscular blockade occurred despite careful train of four monitoring and adjustment of drug infusion. The authors concluded that for infusions of this duration (<2 days), vecuronium is probably more suitable for administration in intravenous bolus doses rather than by infusion in patients with renal and respiratory failure.

In the cases reported here, however, we found increasing requirements for vecuronium over prolonged infusion period of several months. In addition, although full spontaneous recovery period was prolonged for 12 hr, this was rather inconsequential after the long duration of neuromuscular relaxation. Attempts at pharmacological reversal of neuromuscular blockade were not undertaken. This prolonged spontaneous recovery may have been secondary to accumulation of vecuronium or active metabolites in tissue stores during prolonged exposures. Both patients were in dynamic clinical states with variation in temperature, electrolyte balance, volume status, and acid-base function as well as fluctuating end-organ performance. It was not possible to correlate the severity of either patient's condition with the dose required at any given time. Physiological markers such as serum electrolyte levels, blood gas tensions, and liver and renal function were measured at least daily, whereas hemodynamic parameters were under constant evaluation. Pathological changes were treated aggressively and corrected as quickly as possible. However, no consistent physiological alteration was clearly associated with the need for increased vecuronium doses. These two patients required increasing dosages (a 5-6-fold increase) over the time course of drug administration. Both patients received vecuronium continuously for 10-12 weeks. The vecuronium infusions were prepared daily, were refrigerated until used, and were administered within

24 hr. The vecuronium infusions were administered through a dedicated port on a central venous catheter and were not mixed with other drugs. There did not seem to be an identifiable change in vecuronium requirements associated with various drugs administered, which included aminoglycosides, vancomycin, third generation cephalosporins, penicillin derivatives, metronidazole, H-2 receptor antagonists, antacids, and vasoactive drugs (including potent inotropes, vasoconstrictors, or vasodilators). The patients, as expected, did develop tolerance to concurrent sedatives and narcotics believed to reflect alteration in CNS receptor sensitivity as well as enhanced drug metabolism. Respiratory failure was severe in both patients requiring support with ECMO in one patient and serious consideration of ECMO therapy in the other. The patients required prolonged support with high frequency ventilation and PEEP. Both patients developed gram-negative rod and gram-positive coccal sepsis. They suffered moderate to severe dysfunction of additional organ systems, but no direct cause and effect relationship was present regarding dose requirements of vecuronium and multisystem dysfunction.

One possible explanation for the increased dose requirements of vecuronium in these reported patients is the possible proliferation of extrajunctional cholinergic receptors secondary to prolonged nondepolarizing blockade. Proliferation of extrajunctional receptors has been identified as the mechanism of exaggerated response to succinylcholine administration (11). These clinical situations include recent third degree burns, major crush injuries, spinal cord transections, upper motor neuron disorders, and patients with intra-abdominal infections (11,12). Clearly further evaluation and study of this phenomenon of tolerance to vecuronium should be undertaken with measurement of serum levels of vecuronium and its metabolites in patients who develop tolerance while treated with prolonged infusions.

In summary, the patients reported describe our recent experience with long-term infusions of vecuronium in two critically ill patients. These patients required significant and steady increases in the infused dose of vecuronium to maintain adequate relaxation needed to optimize gas exchange. This increased requirement could not be clearly associated with various pathophysiological states, concurrent drug administration, or biochemical abnormalities. These findings are in contradistinction to some of the recent literature regarding the use of vecuronium in the ICU setting and, in particular, in patients with renal insufficiency or failure. Whether this increased requirement is related to an alteration in pharmaco-

kinetics, pharmacodynamics, unrecognized drug interactions, or other factors, remains to be determined. These cases are reported to alert clinicians about this potential increased requirement of vecuronium.

References

1. Smith CL, Hunter JM, Jones RS. Vecuronium infusions in patients with renal failure in an ITU. Anaesthesia 1987; 42:387–93.
2. Noeldge G, Hisken H, Buzello W. Comparison between the continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium. Br J Anaesth 1984;56:473–7.
3. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986;256:881–6.
4. Shanks CA. Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. Anesthesiology 1986;64:72–86.
5. Bevan DR, Donati F, Gyasi H, Williams A. Vecuronium in renal failure. Can Anaesth Soc J 1984;31:491–6.
6. Lebrault C, Berger JL, d'Hollander AA, Gomeni R, Hazel D, Duvaldstein P. Pharmacokinetics and pharmacodynamics of vecuronium (ORG45) in patients with cirrhosis. Anesthesiology 1985;62:601–5.
7. Lynam D, Cronnelly R, Kay P, et al. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. Anesthesiology 1988;69:227–31.
8. Duvaldstein P, Henzel E. Binding of tubocurarine, fazadinium, pancuronium, and ORG 45 to serum proteins in normal man and in patients with cirrhosis. Br J Anaesth 1982;54:513–6.
9. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of ORG NC45 (Norcuron): a new nondepolarizing muscle relaxant. Anesthesiology 1981; 55:6–11.
10. McIndewar IC, Marshall RJ. Interactions between the neuromuscular blocking drug Org NC45 and some anesthetic, analgesic, and antimicrobial agents. Br J Anaesth 1981;53:785–91.
11. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.
12. Kohlschutter B, Baur H, Roth R. Suxamethonium-induced hyperkalemia in patients with severe intra-abdominal infections. Br J Anaesth 1976;48:557–61.

Unintentional Dural Puncture and Prophylactic Epidural Blood Patch in Obstetrics

Pietro Colonna-Romano, MD and Bryan E. Shapiro, MD

Unintentional dural puncture (UDP) is an uncommon but distressing complication of lumbar epidural analgesia. Conservative measures (hydration, bed rest, and the use of an abdominal binder) have been employed to prevent postdural puncture headache (PDPH) after UDP. More invasive techniques including lumbar or caudal epidural injection of saline solution have also been advocated (1–3). The ability of these measures to prevent PDPH is low (4). The use of epidural blood patch (EBP) as treatment of PDPH was suggested by Gormley (5) and later introduced by Di Giovanni and Dunbar (6). The success rate approaches 91% to 100% in many studies (4).

We conducted a prospective sequentially randomized study to compare the efficacy of a prophylactic epidural blood patch (PEBP) with conservative measures in preventing PDPH in obstetrical patients.

Methods

This study was approved by the Human Research Committee of our institution. All patients were selected from the obstetric service after an UDP during placement of a lumbar epidural catheter either for analgesia during labor or for cesarean section. Informed consent was then obtained. Patients with a history of recent or recurrent headache were excluded from the study.   ^

Evidence of dural puncture was clinically assessed by the attending anesthesiologist or, if there was any doubt, by the presence of glucose in material aspi-

rated through the epidural needle. In all instances a 17-gauge Touhy epidural needle was used. After clear evidence of UDP the epidural needle was reinserted and the catheter placed one interspace above. Each patient was then randomly assigned to the control group (CG) or to the study group (SG).

Nineteen parturients entered the SG; 14 were in labor at the time of the dural puncture, and five were not. All were given a PEBP (15 mL of autologous blood under sterile conditions) via the epidural catheter within 2 to 14 hr after the UDP and always after the delivery. The epidural catheter was then removed. No specific instructions were given to these parturients. None of these patients reported headache before the PEBP.

Twenty parturients entered the CG; 16 were in labor at the time of the dural puncture and four were not. In these patients the catheter was removed at the end of the surgical procedure, and they were instructed to drink fluids and avoid ambulation as long as possible. Compliance to this protocol was not enforced.

All patients in both groups were followed for 4 days after the dural puncture. The possibility of headache was mentioned to all patients at the time of the dural puncture. When the patient developed headache while still in the hospital, the obstetrical nurse alerted us of the problem. She was unaware of the treatment. The diagnosis was then confirmed by the anesthesiologist who was not blinded to the patient's group. Patients who were discharged were followed by daily telephone calls. If headache was present the patient was also asked to grade its severity on a subjective mild-moderate-severe scale. The incidence and severity of headache were then compared in the two groups.

Results

Sixteen (80%) of the 20 patients in the CG developed headache. Seven eventually had an epidural blood

patch (EBP) (35%), six had oral medications, and three refused any form of treatment. In this group headache was rated severe or moderate. It was never rated as mild.

In the SG only four of the 19 patients (21%) developed PDPH. Headache was successfully treated with a second EBP in three of these patients. The other patient refused treatment. When it occurred, headache was rated as severe by the four patients.

The incidence of PDPH between the two groups as analyzed by χ^2 analysis was significantly different ($P < 0.005$).

Discussion

EBP is an accepted method of treating PDPH once the symptoms appear. This technique is employed whether the dural puncture is intentional, as in spinal anesthesia, or unintentional, as a complication of lumbar epidural analgesia. Several studies have since demonstrated the efficacy and safety of EBP (7). The traditional approach to the treatment of patients who have suffered an UDP is to wait for the appearance of the characteristic symptoms of PDPH (i.e., headache that is postural in nature) before the institution of therapy.

Prevention of PDPH by the use of a PEBP has been reported by Quaynor and Corbey (8) to be successful in seven nonobstetric patients. Ackermann (9) reported the successful prevention of PDPH in six obstetrical patients who suffered an UDP. He injected 15 mL of autologous blood via the epidural catheter 20 min after delivery. There was no control group.

Our study showed that the incidence of PDPH decreased from 80% to 21% by injecting 15 mL of autologous blood via the epidural catheter a few hours after the completion of the surgical procedure. This amount of blood was used based on the data of Palahniuk and Cumming (10), who failed to prevent PDPH by using only 5-10 mL, and on data by Szeinfeld, who suggested that a volume of 12-15 mL is needed to produce a satisfactory epidural blood patch (11). There were no complications associated with this technique.

It is of interest to note that in all our patients who developed PDPH after a failed PEBP the headache was severe. This suggests that the success of a PEBP may be related to its ability to stop the dural leak; this, in turn, may be an all-or-none phenomenon (i.e., the prophylactic patch may stop the dural leak and thus prevent headache, or it may fail and not affect the severity of the resultant headache at all). Variables that may influence the success rate are the amount of blood

actually covering the dura opening, the pressure gradient between the subarachnoid and the epidural space, and differing sizes of the dural tear.

After an UDP it is common practice to wait for the appearance of symptoms before instituting any therapy, on the grounds that headache may not develop. Even though this approach may be acceptable in the general population, the risk of PDPH in parturients is substantially greater than it is in other patients, and in this population headache is more likely to be severe and debilitating, with an incidence ranging from 76% to 85% (3,12). In many instances a conservative approach will only delay effective treatment.

In summary a prophylactic epidural blood patch, with 15 mL of autologous blood, is a simple and safe technique associated with a good success rate (80%) in preventing postdural puncture headache. It avoids the risk associated with another epidural puncture should an epidural blood patch be necessary. Because of its simplicity, efficacy, and freedom from complications, this technique is recommended in the prevention of postdural puncture headache of this type.

References

1. Rice GG, Dobbs CH. The use of peridural and subarachnoid injection of saline solution in the treatment of severe post spinal headache. Anesthesiology 1950;11:17–23.
2. Crawford SJ. The prevention of headache consequent upon dural puncture. Br J Anaesth 1972;44:598–600.
3. Craft JB, Epstein BS, Coakley CS. Prophylaxis of dural puncture headache with epidural saline. Anesth Analg 1973;52:228–31.
4. Philip BK. Complications of regional anesthesia for obstetrics. Regional Anesth 1983;8:17–30.
5. Gormley JB. Treatment of post spinal headache. Anesthesiology 1960;21:565–6.
6. DiGiovanni AJ, Dunbar BS. Epidural injections of autologous blood for post lumbar puncture headache. Anesth Analg 1970;49:268.
7. Crawford SJ. Experiences with epidural blood patch. Anaesthesia 1980;35:513–5.
8. Quaynor H, Corbey M. Extradural blood patch—Why delay? Br J Anaesth 1985;57:538–41.
9. Ackerman WE, Colclough GW. Prophylactic epidural blood patch: the controversy continues (letter). Anesth Analg 1987;66:913.
10. Palahniuk RJ, Cumming M. Prophylactic blood patch does not prevent post lumbar puncture headache. Can Anesth Soc J 1979;26:132–3.
11. Szeinfeld M, Ihmeidan I, Moser M, et al. Epidural blood patch: evaluation of the volume and the spread of blood injected into the epidural space. Anesthesiology 1986;64:820–2.
12. Brownridge P. The management of headache following dural puncture in obstetric patients. Anaesth Intensive Care 1983;11:4–16.

Atrioventricular Mobitz I Block during Propofol Anesthesia for Laparoscopic Tubal Ligation

Marie-France Ganansia, MD,* Thierry P. Francois, MD, Xavier Ormezzano, MD,*
Michel L. Pinaud, MD, PhD, and Jean-Yves Lepage, MD

Key Words: ANESTHETICS, INTRAVENOUS—propofol.

Propofol (2,6–diisopropyl phenol) dissolved in an emulsion formulation has been introduced for the IV induction and maintenance of general anesthesia (1). In contrast to other intravenous and inhalation anesthetics, it does not depress the baroreflex sensitivity. Through central vagotonic and/or sympatholytic mechanisms, it resets the baroreflex, resulting in slower heart rates despite decreased arterial pressures (2). When propofol is combined with opioids such as fentanyl, the slowing of heart rate may be even greater (2).

The present report describes the occurrence of a second degree atrioventricular Mobitz I block during general anesthesia with propofol in combination with fentanyl and vecuronium in two patients undergoing laparoscopy for tubal ligation.

Case Reports

Two healthy women (36 and 39 years old) ASA physical status I were scheduled for tubal ligation. Neither had a history of cardiac rhythm disturbance. They both underwent gynecologic surgery in our institution a few years ago, under general anesthesia without complications. Their preoperative laboratory results were within the normal range and their ECG was normal. They were not receiving any medications. Midazolam 5 mg IM was given 30 min before surgery. Before induction, blood pressure was respectively 129/71 and 110/60 mm Hg, heart rate 67

and 100 beats/min with sinus rhythm. Blood pressure and ECG were monitored throughout the procedure. In each case, anesthesia was induced with propofol 2 mg/kg of body weight as a bolus, and fentanyl 2 μg/kg. Orotracheal intubation was performed after 70 μg/kg vecuronium bromide. A propofol infusion was started at a rate of 10 mg·kg^{-1}·hr^{-1} for 5 min and then at 6 mg·kg^{-1}·hr^{-1} until the end of surgery. Respirations were controlled during 70%/30% nitrous oxide-oxygen administration. After tracheal intubation, blood pressure and heart rate were respectively 107/59 and 99/55 mm Hg and 71 and 85 beats/min. Carbon dioxide peritoneal insufflation was done, the patient being in the Trendelenburg position, until an intra-abdominal pressure of 15 mm Hg was reached. During insufflation, the ECGs in both patients showed first a sinus bradycardia and then a second degree atrioventricular Mobitz I block without any blood pressure change. The ECG was recorded on a paper strip, and after a few seconds, 1 mg IV atropine was administered as a bolus. In both cases, sinus rhythm was reestablished within 30 sec. Anesthesia and surgery proceeded then uneventfully. The postoperative ECG were normal. Holter ambulatory monitoring of electrocardiogram for 24 hr a month postoperatively in both patients showed no abnormalities nor bradycardia, no lenghtened PR intervals nor second degree atrioventricular Mobitz I block.

Discussion

Atrioventricular Mobitz I block may be seen in about 6% of healthy asymptomatic young adults (3). The conduction defect is located on the atrioventricular node. The block usually disappears with atropine or exercise. The decreased conduction through the atrioventricular node is probably due to increased vagal tone (3). In our two patients, the preoperative ECG was normal and postoperative Holter monitoring showed no conduction abnormalities.

Atrioventricular Mobitz I block is a rather unusual complication during general anesthesia (4). However, drugs used in the two cases described here may have a direct or indirect effect on conduction. Fentanyl is a vagotonic opioid that stimulates the central vagal nucleus (5), and it probably possesses the same direct depressing effect on the sinoatrial node and the atrioventricular conduction as morphine does (5,6). Propofol lacks vagolytic activity and may produce a central vagotonic or sympatholytic effect, or both (2). The mechanism of its direct action on the sinus node and atrioventricular conduction is unclear. At concentrations used clinically, propofol appears to have a direct negative effect on sinus activity with no effect on atrioventricular conduction in animals (7). Severe bradycardia and arrhythmias have been described with propofol (8–10). When the combination of propofol and fentanyl is used, propofol blood concentrations are greater than those resulting from the use of propofol alone (11). Therefore, fentanyl may potentiate the action of propofol on the heart. Vecuronium lacks cardiovascular effects (12), including vagal blocking activity (13). Bradycardia and several cases of cardiac arrests with vecuronium, however, have been reported (14,15).

On the basis of the pharmacological properties of the drugs used in the present two cases, it can be assumed that occurrence of atrioventricular block in our patients after a premedication that did not include atropine was probably secondary to an increase in vagal tone due to propofol and fentanyl during surgery associated with parasympathetic stimulation (16). Vecuronium did not provide a protection against this increased vagal activity as pancuronium might have done. In both patients, the atrioventricular block terminated immediately after IV atropine.

Propofol may well have been the triggering factor in the atrioventricular block seen in our two patients. We perform 300 laparoscopies a year in our institution with thiopental, fentanyl, vecuronium, and without any parasympatholytic premedication with no instances of atrioventricular block before the use of propofol.

In conclusion, during surgical procedures associated with vagal stimulation, one should be cautious in combining fentanyl and vecuronium with propofol. When such a combination of drugs is to be used adequate anticholinergic premedication is in order.

References

1. Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion of ICI 35868 (propofol) for the induction and maintenance of anaesthesia. Br J Anaesth 1985;57:736–42.

2. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987;66:1115–20.

3. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hours continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 1977;39:390–5.

4. Russell PH, Coakley CS. Electrocardiographic observation in the operating room. Anesth Analg 1969;48:784–8.

5. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiology 1984;61:731–55.

6. Royster RL, Keeler DK, Haisty WK, Prough DS, Johnston WE. Effect of fentanyl and neuromuscular blockers on atrioventricular conduction times in dogs. Anesthesiology 1985;63:A78.

7. Colson P, Barlet H, Roquefeuille B, Eledjam JJ. Mechanism of propofol bradycardia. Anesth Analg 1988;67:906–7.

8. Baraka A. Severe bradycardia following propofol—suxamethonium sequence. Br J Anaesth 1988;61:482–3.

9. Henriksson BA, Carlsson P, Hallen B, Hagerdal M, Lundberg D, Ponten J. Propofol vs thiopentone as anaesthetic agent for short operative procedures. Acta Anaesthesiol Scand 1987; 31:63–6.

10. Thomson SJ, Yate PM. Bradycardia after propofol infusion. Anaesthesia 1987;42:430.

11. Briggs LP, White M, Cockshott ID, Douglas EJ. The pharmacokinetics of propofol (diprivan) in female patients (abstr). Postgrad Med J 1985;61(suppl 3):58–9.

12. Booij LHDJ, Edwards RP, Sohn YJ, Miller RD. Cardiovascular and neuromuscular effects of org NC 45, pancuronium, metocurine and d-tubocurarine in dogs. Anesth Analg 1980;59: 26–30.

13. Barnes PK, Brindle Smith G, White WD, Tennant R. Comparison of the effects of org NC 45 and pancuronium bromide on heart rate and arterial pressure in anaesthetized man. Br J Anaesth 1982;54:435–9.

14. Milligan KR, Beers HT. Vecuronium—associated cardiac arrest. Anaesthesia 1985;40:385.

15. Kirkwood I, Duckworth RA. An unusual case of sinus arrest. Br J Anaesth 1983;55:1273.

16. Smith BE. Anesthetic emergencies. Clin Obstet Gynecol 1985; 28:391–404.

Hemoptysis in a Child during Extracorporeal Shock Wave Lithotripsy

Vinod Malhotra, MD, Matthew C. Gomillion, MD, and Joseph F. Artusio JR, MD

Key Words: ANESTHESIA, UROLOGIC—lithotripsy.

Extracorporeal shock wave lithotripsy (ESWL) using a Dornier HM-3 lithotripter is commonly employed for disintegration of upper urinary tract stones in adults. Its use has been extended to the treatment of kidney stones in children. In the Dornier HM-3 lithotripter, the patient is strapped in a gantry chair and submerged from the clavicle down in water in a large immersion tub. The shock waves are generated under water and passed through the patient's flank to be focused on the kidney stone. After release of most of their energy at the stone, the shock waves exit through the upper abdomen. The renal and surrounding tissues are quite resistant to damage by the shock waves; therefore, the normal passage of shock waves during lithotripsy rarely produces any significant damage other than ecchymoses or hematuria. However, the lung is prone to extensive damage if exposed to the shock waves (1). This potential for pulmonary damage is greater in children because of the closer proximity of their lung bases to their kidneys when compared with adults. We report a case of a 3-year-old child who suffered hemoptysis during ESWL.

Case Report

A 3-year-old white female patient, weighing 11.6 kg, was scheduled for ESWL of a left renal stone. She had been diagnosed to have von Gierke's disease (Type I glycogen storage disease, hepatorenal glycogenosis) and was being treated with allopurinol, Bactrim (trimethoprim and sulfamethoxazole) and iron supplements. Physical examination was notable for a grossly distended abdomen and marked hepatomeg-

aly. Preoperative laboratory tests revealed a mildly elevated prothrombin time of 12.9 sec (normal value 9–12 sec) with a normal activated partial thromboplastin time of 33.6 sec (normal 23–38 sec) and a platelet count of $788,000/mL^3$. Urinalysis showed 5–10 red cells and 15–20 white cells/hpf.

On the morning of the procedure, the patient was transported to the lithotripsy suite with a peripheral intravenous infusion of 10% dextrose in 0.3 N saline running well. After placement of an electrocardiograph (ECG), a blood pressure cuff, a pulse oximeter, and a precordial stethescope, general anesthesia was induced smoothly with thiopental sodium, 3 mg/kg, followed by succinylcholine, 1 mg/kg, to facilitate laryngoscopy. Under direct visualization of the larynx, the trachea was easily and atraumatically intubated with a 4.5-mm endotracheal tube. After securing the endotracheal tube in place and confirming the presence of bilaterally equal breath sounds, the administration of halothane and nitrous oxide was started. The patient was then transferred to the modified hydraulic lift system of the Dornier HM-3 lithotripter and immersed in the water bath. No coughing or reacting to the endotracheal tube occurred during this transfer. Bilaterally equal breath sounds were reconfirmed by ausculation.

Forty minutes after the induction of general anesthesia, ESWL was started with impulses delivered at 18 kV. About 3 min later when 350 impulses had been delivered, the anesthesiologist noted a small amount of bright red blood in the endotracheal tube. Lithotripsy was discontinued and 100% oxygen was administered. Suctioning of the endotracheal tube yielded approximately 3–4 mL of bright red blood; no blood was present on suctioning of the mouth or pharynx. The patient was removed from the water bath and given 100% oxygen. Further suctioning of the endotracheal tube yielded no more blood. During the episode, pulse oximeter readings remained at 100%. When awake, the patient was extubated without difficulty and subsequently transported to the recovery room. Examination of the shock wave entry

site in the left flank revealed no ecchymosis or hematoma. Chest x-ray film in the recovery room showed the lungs to be clear. Postoperatively, the patient did well with no signs of further bleeding and no evidence of respiratory distress. Because the patient was asymptomatic, the parents refused any further tests and she was discharged the following day.

One month later the child was readmitted because the stone had moved down into the ureter causing obstruction. Her general medical condition was otherwise unchanged since her previous admission. She underwent a laser lithotripsy under general endotracheal anesthesia with isoflurane, nitrous oxide, and oxygen without any untoward event. Her postoperative course was unremarkable, and she was discharged from the hospital the following morning.

Discussion

Shock waves are generated under water in the Dornier HM-3 lithotripter and need to be transmitted through water because the acoustic impedance of water is similar to that of the body tissues. This procedure allows shock wave propagation through tissues without dissipation of energy, thus avoiding tissue injury. Because of the physical characteristics of the shock waves, when an interphase such as water–stone is encountered, the shock wave energy is dissipated in the form of mechanical stress to the order of several hundred atmospheres, causing stone disintegration. Similarly, when the shock waves encounter a tissue (water)–air interphase, the release of shock wave energy at the interphase will result in tissue injury. Lungs, being air filled sacs, provide such an interphase. Massive hemoptysis and death from pulmonary damage due to vascular and alveolar rupture has been reported in laboratory animals after a single exposure of the thoracic region to shock waves (1). This potential of shock waves to cause pulmonary damage poses a real problem during lithotripsy in children because of the close proximity of the kidneys to the lungs.

The lung bases, especially in children, need to be protected from the shock waves during lithotripsy. Animal experiments have demonstrated that a 3-mm thick styrofoam sheet blocks the shock waves completely (1). Therefore, it has been recommended that in children, a styrofoam sheet or a board placed under the patient's back in a manner such as to shield the lung bases from shock waves be used during ESWL (2). In several children, over the last 4 years, we have successfully employed a 4-cm thick styro-

Figure 1. The styrofoam board (arrows) placed under the child's back provides back support as well as lung protection from shock waves.

foam board placed behind the upper back of the patient for this purpose. The styrofoam board (conveniently obtained from the protective packing of a box of Dornier electrodes) provides the much needed extension of the back support of the gantry chair for the pediatric patient while protecting the lung bases (Figure 1).

In this particular case, the styrofoam board was omitted. Instead, airbags filled with styrofoam pastilles and attached to a mat were placed behind the patient's back to protect the lung bases from the shock waves. We believe that these airbags floated out of position once the patient was immersed in water, leaving the lung bases unprotected, resulting in hemoptysis. After this episode, we promptly resumed the earlier practice of using the styrofoam board to protect the lung bases in children undergoing lithotripsy. No other incident of hemoptysis before this case or after this case has occurred in our experience with over 30 children undergoing lithotripsy with the lung bases protected by the styrofoam board.

Von Gierke's disease is caused by a deficiency of glucose 6-phosphatase resulting in glycogen storage, fasting hypoglycemia, hyperlipidemia and hyperuricemia with a clinical picture of a large protuberant abdomen, and hepatomegaly, a gouty syndrome and often a coagulopathy that usually occurs after 2 years of age (3). It seems unlikely that a coagulopathy resulted in hemoptysis in this case for the following reasons. First, the child had no past history of abnormal bleeding tendency; in fact, there was no gross hematuria reported despite the presence of a renal stone. Second, no ecchymosis or hematoma was observed at the shock wave entry site as one might expect if the patient were to have a significant coagulopathy. Finally, the hemoptysis occurred within 3

min of the initiation of the shock waves at which time no endotracheal movement was taking place. This convinces us that the shock wave induced injury was the most likely cause of hemoptysis in this case.

We believe this case to be the first published report of hemoptysis occurring in a child during renal lithotripsy, although the potential danger of this problem has been fairly well described on the basis of animal experiments. It underscores the importance of taking extreme care in protecting the lung bases in children during lithotripsy. Based on our experience, we recommend that the anesthesiologist should see to it that a styrofoam protective device is in place in children and stays in place during positioning and immersion for ESWL. In addition, when the stone is being positioned in the shock wave focus with use of fluoroscopy, the child's respirations should be observed on the fluoroscope to further ensure that the lung bases are not in the blast path of the shock wave. We believe that these steps are necessary to prevent shock wave induced lung injury in children during ESWL.

References

1. Chaussy CG. Extracorporeal Shock Wave Lithotripsy: New Aspects in the Treatment of Kidney Stone Disease. Munich: Karger, 1982:24-35.

2. Tredrea CR, Pathak D, From RP, Grucza J. Lung protection in children during extracorporeal shock wave lithotripsy. Anesth Analg 1987;S178.

3. Sidbury JB. The Glycogenoses. In: Rudolph AM, Hoffman JIE, eds. Pediatrics. Norwalk: Appleton-Century-Crofts, 1982:291-2.

Thoracic Epidural Anesthesia for Transsternal Thymectomy in Myasthenia Gravis

Frederick W. Burgess, PhD, MD and Bernard Wilcosky Jr, MD

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—thymectomy. COMPLICATIONS, MYASTHENIA GRAVIS.

Myasthenia gravis is an autoimmune disorder characterized by varying degrees of muscle weakness, progressive muscle fatigue, ptosis, ophthalmoplegia, and bulbar symptoms secondary to destruction of postsynaptic acetylcholine receptors (1). Although infrequently encountered—prevalence is estimated to be 1 in 20,000—patients with myasthenia gravis represent a significant management problem for the anesthesiologist (1). Anesthetic concerns center on the myasthenic patient's unpredictable response to skeletal muscle relaxants and potential for postoperative respiratory failure resulting in prolonged dependence on mechanical ventilation (2–5). Early surgical intervention in the form of transcervical or transsternal thymectomy has become a mainstay in the aggressive management in selected patients with myasthenia gravis (6–8). Although controversy persists over the risks and benefits of the transcervical and transsternal thymectomy approaches with regard to long-term outcome, it is clear that the transthoracic approach carries a greater risk of postoperative respiratory compromise (4,5,7). In this case report we describe the use of a thoracic epidural anesthetic in combination with a light general anesthetic to provide excellent surgical conditions and improved postoperative analgesia in two patients with progressive stage IIa myasthenia gravis undergoing transsternal thymectomy.

Case Reports

Case 1

A 24-year-old black woman, who, at 4 years of age, had had ocular myasthenia gravis diagnosed by a positive edrophonium (Tensilon) test, was to undergo a transsternal thymectomy for progressive myasthenia gravis. Past medical history was significant for Graves' disease requiring ablative therapy with radioactive iodine and an admission to the intensive care unit following rapid progression of her myasthenia gravis. Following the institution of plasmapheresis, her myasthenia gravis stabilized.

Approximately 6 months after stabilization of her Graves' disease, this patient was preoperatively evaluated for a transsternal thymectomy. Her medications included pyridostigmine, 60 mg, five times daily plus 180 mg of the slow-release form at bedtime; levothyroxine, 0.15 mg, daily; and prednisone, 80 mg, every other day. Physical examination revealed a slender black woman with marked ptosis, ophthalmoplegia, and bilateral proptosis. Blood pressure was 85/50 mm Hg, pulse 80 beats/min, and respirations 16 breaths/min. Preoperative forced vital capacity (FVC) was 3.01 L with a 1-sec forced expiratory volume (FEV1) of 2.92 L. Results of thyroid function tests and routine preoperative laboratory studies were within normal limits. She continued her usual medications preoperatively, including the morning of surgery, along with a dose of triazolam, 0.125 mg.

On the patient's arrival in the operating room, 16-gauge intravenous and 20-gauge radial artery catheters were inserted. Standard monitors included electrocardiogram, esophageal stethoscope, and pulse oximeter. With the patient in the sitting position a thoracic epidural catheter was placed via the T6-T7 interspace using the loss of resistance technique with an 18-gauge Tuohy needle. The epidural catheter

passed easily without paresthesias or return of blood or cerebrospinal fluid. The patient was then placed in the supine position and a 3-mL test dose of 1.5% lidocaine with 1:200,000 epinephrine was injected into the epidural catheter without evidence of intravascular injection or subarachnoid block. General anesthesia was then induced, after preoxygenation with 100% oxygen (O_2), with thiopental, 2 mg/kg, and fentanyl, 5 μg/kg. Assisted ventilation was continued for 5 min with 2% isoflurane and 100% O_2, followed by a second 2 mg/kg injection of thiopental. Laryngoscopy was performed and the trachea intubated without difficulty using a 7.0 styleted endotracheal tube under direct vision. Following intubation, 2 to 3 mL of 2% lidocaine plus 1 mL fentanyl (50 μg) were injected into the epidural catheter for a total of 11 mL over a 15-min period. General anesthesia was maintained with 65% nitrous oxide, 35% O_2, and 0.2% isoflurane. Following induction, the patient's blood pressure remained within 10% of her normal pressure (90/60 mm Hg), with a pulse rate of approximately 90 beats/min. There was no hemodynamic response to skin incision or sternotomy. The only hemodynamic changes occurred with dissection into the neck in the C3 dermatome. Additional 2 to 3 mL of 2% epidural lidocaine were injected every 30 min until 30 min prior to the completion of surgery for a total volume of 17 mL. Total operating time was 2 hr 22 min. Estimated blood loss was 250 mL. Intraoperative fluid administration included 2,700 mL lactated Ringer's solution. On completion of the transsternal thymectomy the patient was transported anesthetized and intubated to the postanesthesia intensive care unit (ICU).

On arrival in the ICU, 100 μg of fentanyl in 10 mL 0.9% sodium chloride (NaCl) was injected epidurally followed by a continuous epidural infusion of fentanyl (4 μg/mL) in 0.9% NaCl. Over the course of 90 min, the patient recovered from the general anesthesia, while mechanical ventilation was gradually withdrawn using the intermittent mandatory ventilation mode. Following demonstration of a maximal inspiratory pressure of −40 mm Hg, the patient's trachea was uneventfully extubated. Preoperative medications, including pyridostigmine, were resumed on the afternoon of surgery. The patient was allowed out of bed to a chair that afternoon, where she visited with friends and relatives without pain. She remained pain-free overnight in the ICU, during which she had a continuous epidural infusion of fentanyl at 48 μg/hr (12 mL/hr). On postoperative day 1 the patient was transferred to the open ward where she continued to do well. Pathologic evaluation of the surgical specimen revealed normal thymic tissue.

Case 2

A 43-year-old white woman presented for excision of an anterior mediastinal mass through a transsternal thoracotomy. Her medical history was notable for recent onset of Graves' disease and myasthenia gravis 6 months prior to admission. The patient denied a history of respiratory illness, and the results of her pulmonary function studies were within normal limits. Preoperative medications included methimazole, 30 mg, daily; pyridostigmine, 60 mg, four times daily; and propranolol, 20 mg, four times daily. Physical examination revealed a middle-aged moderately obese woman with an enlarged nontender thyroid gland and minimal motor weakness. On the morning of surgery, she was given triazolam, 0.125 mg, in addition to her usual medications listed above. On arrival in the operating room, 16-gauge intravenous and 20-gauge radial artery catheters were inserted, followed by placement of an epidural catheter as described above. General anesthesia was induced, following a 50-mg IV injection of thiopental, by inhalation of O_2 and isoflurane. After a second IV injection of thiopental the trachea was easily intubated. Controlled ventilation was established and anesthesia maintained with 0.6–0.8% isoflurane. Following a test dose of 3 mL lidocaine 1.5% with 1:200,000 epinephrine, incremental epidural injections up to a total of 10 mL of 2% lidocaine were made. Arterial blood pressure remained within 20% of her normal pressure. She had no response to surgical stimuli. Operating time was 95 min, and the patient received 3300 mL of lactated Ringer's solution with a blood loss of 380 mL. At the completion of surgery, the patient was given, via the epidural catheter, 75 μg of fentanyl diluted in 10 mL of 0.9% NaCl. Tracheal extubation was performed uneventfully in the operating room, and the patient was taken to the ICU spontaneously ventilating with supplemental O_2. In the ICU a continuous epidural infusion of fentanyl was initiated at 10 mL/hr (4 μg/mL) with excellent results. The patient was transferred to the open ward 24 hr later. Pathologic evaluation of the surgical specimen revealed a large thymoma.

Discussion

Myasthenia gravis is a disease characterized by progressive muscle weakness and eventual respiratory failure (1,6). This disorder appears to be mediated by a defect in autoregulation of the immune system that results in destruction of postsynaptic acetylcholine receptors, often concomitant with other disorders of

the immune system, e.g., Graves' disease. Standard treatment of myasthenia gravis has focused on augmenting cholinergic function with acetylcholinesterase inhibitors. High-dose steroid therapy and immunosuppression with antimetabolites has had only limited success in altering the progression of the underlying disease process. Plasmapheresis is a useful short-term option in treating acute exacerbations prior to more definitive therapy. In recent years, thymectomy has become increasingly regarded as a means to achieve prolonged remission, and clinical improvement is reported to be 70% to 90% with thymectomy (1,6–8). As to the surgical approach to thymectomy, the transcervical thymectomy has been touted as being equally efficacious in providing long-term remission with an incidence of postoperative morbidity and respiratory complications lower than those seen with the standard transsternal approach (7). Others have argued for the transsternal approach as the method providing the most complete removal of the thymus gland (8). Progression of symptoms and regeneration of thymic tissue have been reported with both techniques.

Anesthetic considerations in the myasthenic patient include a marked sensitivity to nondepolarizing skeletal muscle relaxants, the potential interaction of acetylcholinesterase inhibitors with both the depolarizing and nondepolarizing muscle relaxants, and the increased risk of perioperative respiratory insufficiency requiring prolonged intubation. It is generally agreed that muscle relaxants are best avoided altogether. Several recent studies have suggested a role for the new shorter-acting agents (atracurium and vecuronium) (9,10). However, it still seems prudent to avoid muscle relaxants unless absolutely necessary. Many patients with advanced stages of myasthenia gravis behave as though already under the effect of curare (11). For patients presenting in the early stages of myasthenia gravis, who require muscle relaxation for surgery, we recommend some form of regional anesthesia. The concept of thoracic epidural anesthesia for intrathoracic surgery has been extensively employed and reviewed by Crawford and associates (12).

As these case reports demonstrate, thoracic epidural anesthesia can be beneficially employed as the primary anesthetic for transsternal thymectomy. In combination with a light general anesthetic for patient comfort, the thoracic epidural technique pro-

vided optimal operating conditions, including muscle relaxation, and facilitated postoperative recovery by providing maximal analgesia. A short-acting amide local anesthetic, such as lidocaine, provided rapid titration of the block and minimized the potential interaction of the perioperative acetylcholinesterase inhibitors with metabolism of ester class anesthetics. Gradual establishment of the epidural block with small incremental doses of anesthetic appeared to minimize sympathectomy-related hypotension.

In conclusion, we encourage further study of thoracic epidural anesthesia and analgesia as a method to provide optimal operating conditions and improved patient safety and comfort in patients presenting for transsternal thymectomy in the treatment of myasthenia gravis.

References

1. Seybold ME. Myasthenia gravis: a clinical and basic science review. JAMA 1983;250:2516–21.

2. Leventhal SR, Orkin FK, Hirsh RA. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis. Anesthesiology 1980;53:26–30.

3. Sivak ED, Mehta A, Hanson M, Cosgrove DM. Postoperative ventilatory dependency following thymectomy for myasthenia gravis. Cleve Clin Q 1984;51:585–9.

4. Gracey DR, Divertie MB, Howard FM Jr, Payne WS. Postoperative respiratory care after transsternal thymectomy in myasthenia gravis. A 3-year experience in 53 patients. Chest 1984;86:67–71.

5. Grant RP, Jenkins LC. Prediction of the need for postoperative mechanical ventilation in myasthenia gravis: thymectomy compared to other surgical procedures. Can Anaesth Soc J 1982;29:112–6.

6. Oosterhius HJ. Observation of the natural history of myasthenia gravis and the effect of thymectomy. Ann NY Acad Sci 1981;377:679–90.

7. Papatestas AE, Genkins G, Kornfeld P, et al. Effects of thymectomy in myasthenia gravis. Ann Surg 1987;206:79–88.

8. Fischer JE, Grinvalski HT, Nussbaum MS, Sayers HJ, Cole RE, Samaha FJ. Aggressive surgical approach for drug-free remission from myasthenia gravis. Ann Surg 1987;205:496–501.

9. Baraka A, Dajani A. Atracurium in myasthenics undergoing thymectomy. Anesth Analg 1984;63:1127–30.

10. Buzello W, Noeldge G, Krieg N, Brobmann GF. Vecuronium for muscle relaxation in patients with myasthenia gravis. Anesthesiology 1986;64:507–9.

11. Horowitz SH, Genkins G, Kornfeld P, Papatestas AE. Electrophysiologic diagnosis of myasthenia gravis and the regional curare test. Neurology 1976;26:410–17.

12. Crawford OB, Ottosen P, Buckingham WW, Brasher CA. Peridural anesthesia in thoracic surgery, a review of 677 cases. Anesthesiology 1951;12:73–84.

Esophageal Perforation—a Complication of Neonatal Resuscitation

Julie Topsis, MD, Helen Y. Kinas, MD, and Stephen R. Kandall, MD

Oropharyngeal suctioning and tracheal intubation form critical therapeutic elements in the resuscitation of compromised neonates. These standard procedures reduce both the morbidity and mortality associated with such conditions as perinatal asphyxia and intrapartum fetal meconium passage. Recently, however, the need for aggressive airway management to prevent meconium aspiration has been questioned (1), especially in light of documented morbidity such as laryngeal stridor and residual hoarseness associated with suctioning and intubation. Traumatic perforation of the hypopharynx has also been described following oropharyngeal suctioning at birth to clear secretions or during the passage of an orogastric or nasogastric tube for lavage or decompression (2–5). We present three cases of iatrogenic perforation of the esophagus secondary to upper airway suctioning and/or intubation. Delivery room personnel entrusted with the critical task of neonatal resuscitation must weigh the risks and advantages of these procedures in developing appropriate protocols for the care of compromised newborn infants.

Case Reports

Case 1

The infant was a 2950-g product of a 37 week gestation born by forceps delivery. Apgar scores were 7 at 1 min and 8 at 5 min. After delivery, the infant's oropharynx was suctioned using a stiff tracheal catheter, but suctioning was discontinued due to bradycardia. A nasogastric tube was subsequently easily

inserted for gastric suctioning by a senior resident. In the newborn intensive care unit (NICU), a first nipple feeding at 3 hr of age led to cyanosis, increased oral secretions, and respiratory distress. Chest x-ray at that time was unremarkable. Because of continuing feeding intolerance and mild respiratory compromise, an esophagram was performed on the second day. This was originally interpreted as an esophageal duplication (Figure 1). The following day endoscopy revealed a traumatic ulcerated area in the proximal esophagus and development of a false lumen within the esophageal wall. The infant was treated with antibiotics for 14 days, oral feedings were discontinued, and intravenous alimentation started. At 15 days of age, the esophagram was normal. Feedings were begun that day, advanced slowly and tolerated well. The infant was discharged at 3 weeks of age.

Case 2

The infant was a 3500-g product of a term gestation complicated by the presence of meconium in the amniotic fluid before delivery. Apgar scores were 8 at 1 min and 9 at 5 min. At birth, the infant was intubated by a junior resident using a laryngoscope with a Miller 0 blade with a 3.5 mm Portex tracheal tube with a metal stylet. Suctioning was performed through the tube with an Argyle 8 French polyvinyl suction catheter. An 8 French nasogastric feeding tube was also inserted for gastric lavage. The infant was sent to the regular nursery but was admitted to the NICU at 3 hr of age because of respiratory distress and stridor. Chest x-ray was within normal limits. An initial feeding was followed by regurgitation and increasing respiratory distress. Oral feedings were stopped and the baby was maintained on intravenous alimentation. An esophagram on the first day was initially interpreted as a communicating duplication of the upper two-thirds of the esophagus. Endoscopy performed at 5 days of age revealed a traumatic esophageal opening near the pharyngeal junction. Antibiotics were administered and continued for 14 days. The following day surgical exploration con-
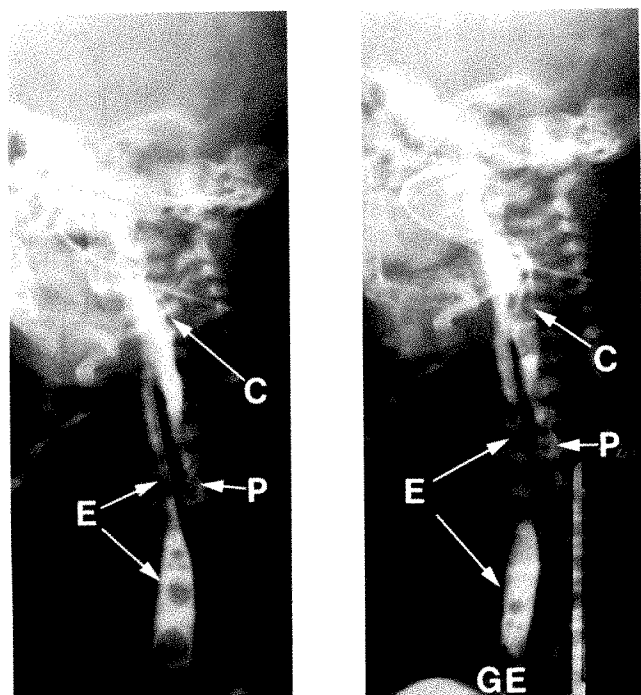
Figure 1. In a right anterior oblique view, contrast material outlines a normal intrathoracic esophagus (E). A perforation is noted at the level of the cricopharyngeal muscle (C) with a long dissection ending as a blind pouch (P) in the posterior mediastinum. Further visualization of the esophagus to the level of the gastroesophageal junction (GE) is also noted.

firmed the finding of a traumatic esophageal perforation with dissection into the esophageal layers. Surgical closure of the perforation was tolerated well. Gastrostomy feedings were begun 4 days postoperatively, and oral feedings were begun on the 7th postoperative day. An esophagram on day 15 revealed a normal esophagus with no extravasation, obstruction, or strictures. The infant was discharged at 3 weeks of age.

Case 3

The infant was a 3280-g product of a term gestation born by cesarean section for failure to progress due to cephalopelvic disproportion. Thick meconium in the amniotic fluid was noted just before delivery. Apgar scores were 7 at 1 min and 8 at 5 min. Immediately after delivery, the infant was intubated easily by a junior resident using a laryngoscope with a Miller 0 blade and a 3.5 mm Portex endotracheal tube through which was passed an 8 French Argyle polyvinyl catheter for tracheal suctioning. An 8 French nasogastric tube was also inserted for gastric lavage. At 11 hr of age the infant was transferred from the regular nursery to the NICU because of stridor and respira-

tory distress. Chest x-ray revealed a lucency adjacent to the cervical portion of the esophagus. At 4 days of age, an esophagram revealed the presence of a retropharyngeal pouch consistent with an esophageal perforation. Oral feedings were stopped and the baby was treated with antibiotics for 10 days, at which time feedings were introduced through a nasogastric tube in place. Nipple feedings were started thereafter and tolerated well. An esophagram at 15 days of age was within normal limits. The infant's stridor disappeared, and she was discharged at 4 weeks of age.

Comment

The need for effective oropharyngeal suctioning and endotracheal intubation in the resuscitation of compromised neonates is unquestioned. It is also crucial, however, that these procedures be carried out skillfully by experienced personnel. In our three cases, iatrogenic perforation of the esophagus occurred in the delivery room following procedures intended to clear the upper airway or stomach of secretions and/or meconium. In all three cases, tracheal intubation, tracheal suctioning, and gastric lavage were carried out by residents in training with varying degrees of experience. No bleeding was evident in the posterior pharynx, and in all three cases the level of concern was low enough to admit the infant to the regular nursery (cases 2 and 3) or to begin oral feedings (case 1).

Most traumatic perforations of the esophagus occur in its cervical portion at the level of the pharyngoesophageal junction proximal to the cricopharyngeal muscle (2,3). At this anatomic point both the cricopharyngeal muscle and the cervical vertebrae may compress the esophageal lumen, predisposing the esophagus to injury by instrumentation. Hyperextending the neck, a common mistake made by the inexperienced during airway manipulation, may further increase the possibility of esophageal injury. Cricopharyngeal spasm induced by direct injury to the posterior pharyngeal wall may make the passage of an endotracheal tube or suction catheter difficult and increase the risk of perforation (2,3). Following cricopharyngeal spasm, subsequent attempts either to intubate or to pass a nasogastric tube may lead to the development of traumatic pseudodiverticula. Cricopharyngeal spasm itself may resemble esophageal atresia, with increased salivation and inability to pass a nasogastric tube. To minimize the risk of spasm, therefore, suctioning should always be performed with soft tubes, and intubation should be performed carefully, avoiding both protruding metal

stylets and blind placement. To minimize trauma, the insertion of nasogastric tubes in the downward rather than posterior direction is preferred.

When esophageal perforation does occur, prompt recognition is essential to reduce the morbidity and mortality associated with this complication of airway management. Such infants present with excessive oropharyngeal secretions, feeding difficulties, and/or respiratory distress often accompanied by stridor. These infants require care in an intensive care unit, withholding of oral feedings, and supportive intravenous alimentation. Since perforations may be accompanied by mediastinitis, hydrothorax, or pneumothorax, broad spectrum antibiotics should be administered for 10 to 14 days. Plain chest x-ray may show a deviated esophagus or nasogastric tube, an aberrant nasogastric tube position (4,5), or a lucency posterior to the esophagus; lateral x-rays of the neck may show this lucency more clearly (case 3). Contrast studies are more useful, often showing a mucosal tear or retropharyngeal collection consistent with laceration, esophageal duplication, or pseudodiverticulum formation (cases 1, 2, and 3). Careful endoscopy will usually establish the definitive diagnosis, as in our three infants. Successful management of esophageal perforations can usually be accomplished medically (cases 1 and 3), but surgery to repair the esophageal laceration has also been successfully employed (case 2). Signs such as mediastinal widening or increasing respiratory distress may merit surgical intervention.

Recent controversy regarding airway management in the delivery room has centered around the need for aggressive management of infants born through meconium-stained amniotic fluid. Although one study indicated that aggressive management reduced morbidity and mortality associated with meconium aspiration (6), another study has questioned the routine need for such active interventions (1). Complications such as esophageal perforations may prompt reevaluation of protocols for management of

meconium in the neonatal airway. Routine suctioning of the oropharynx and nasopharynx before delivery of the shoulders by the obstetrician appears to be extremely useful in reducing the incidence of meconium aspiration (7). Thick meconium in the neonatal pharynx may best be removed by either a mechanical or manual suction apparatus with a large caliber opening to facilitate clearance of particulate matter. An endotracheal tube should then be carefully inserted by a person skilled in intubation, following which suction should be applied directly to the endotracheal tube via an adaptor and regulated wall-suction device, thus avoiding multiple intubations. After this initial standard management, however, further airway care should be evaluated and managed individually by skilled personnel with appropriate equipment to minimize iatrogenic injury to the compromised neonate.

References

1. Linder N, Aranda JV, Tsur M, et al. Need for endotracheal intubation and suction in meconium-stained neonates. J Pediatr 1988;112:613-5.

2. Krasna IH, Rosenfeld D, Benjamin BG, Klein G, Hiatt M, Hegyi T. Esophageal perforation in the neonate: An emerging problem in the newborn nursery. J Pediatr Surg 1987;22:784-90.

3. Lee S, Kuhn J. Esophageal perforation in the neonate. Am J Dis Child 1976;130:325-9.

4. Girdany B, Sieber W, Osman M. Traumatic pseudodiverticulum of the pharynx in newborn infants. N Engl J Med 1969; 280:237-40.

5. Johnson DE, Foker J, Munson DP, Nelson A, Athinarayanan P, Thompson T. Management of esophageal and pharyngeal perforation in the newborn infant. Pediatrics 1982;70:592-6.

6. Gregory GA, Gooding CA, Phibbs RH, Tooley WH. Meconium aspiration in infants: A prospective study. J Pediatr 1974; 85:848-52.

7. Carson BS, Simmons MA, Bowes WA. Meconium aspiration syndrome following cesarean section. Am J Obstet Gynecol 1978;130:596-7.

Management of a Newborn Infant with Congenital Laryngeal Atresia

Sumio Hoka, MD, Michiko Sato, MD, Junichi Yoshitake, MD, and Jeoji Kukita, MD

Resuscitation of the newborn infant delivered by cesarean section is a challenge for an anesthetist. Tracheal intubation is often necessary to facilitate ventilation. However, difficulty in intubation is not uncommon and can arise either from inability to visualize the larynx and/or from difficult passage of the tube into the trachea. When the larynx is completely obstructed, the only measure by which to save the newborn is emergency tracheotomy. To date, there have been no reports from anesthetists facing the difficulty associated with management of congenital laryngeal atresia. We describe management of a newborn infant delivered by cesarean section who had congenital laryngeal atresia and required tracheotomy immediately after the birth.

Case Report

A male infant weighing 2285 g was delivered after 37 weeks of gestation from a 35-year-old para 3 gravida 3 mother by cesarean section under epidural anesthesia. Her previous delivery was also by cesarean section. Congenital malformations were not anticipated at the time of delivery.

Immediately after birth, the infant became cyanotic with progressive retraction of the chest wall and no audible breath sounds. Apgar scores were 2 at 1 min and 1 at 5 min. Tracheal intubation was attempted but was unsuccessful because of an obstruction at the laryngeal level. An emergency tracheotomy was performed by an anesthetist with ventilation established 15 min after birth and prompt improvement in heart

rate and color. Mechanical ventilation was initiated and the patient was monitored in the neonatal intensive care unit. A flaccid thin abdominal musculature was the only other abnormal finding. An arterial blood gas analysis 1 hr after birth revealed pH of 7.10, Pco_2 of 58 mm Hg, Po_2 of 292 mm Hg and base excess of -13 mEq/L.

Direct laryngoscopies were performed at the ages of 9 days and 3 months and revealed laryngeal atresia. The hypopharynx appeared normal with normal development of the epiglottis. There was no evidence of true vocal cords. The arytenoid cartilages as well as the paired intrinsic muscles were fused across the midline. The pharyngotracheal duct was seen in the posterior commissure. The magnetic resonance imaging (MRI) of the head, neck, and thorax revealed glottic and subglottic atresia (Figure 1).

The patient has no obvious neurological defects to date (10 months of age). It is expected that surgical correction of laryngeal atresia will be performed at a later time.

Discussion

Rossi (1) described the first case of laryngeal atresia in 1826, and 51 cases have subsequently (up to 1987) been reported in the literature (2). The diagnosis was established in most cases at autopsy (3,4). Although congenital atresia is regarded as the rarest of the congenital stenotic lesions of the larynx (5), the true incidence is unknown, many such deaths being attributed to stillbirth or neonatal asphyxia. Anesthetists, however, must be aware of this congenital anomaly because of the importance of prompt recognition and treatment.

Smith and Bain (3) classified the congenital laryngeal atresia into three types: Type 1, in which the supraglottic and infraglottic parts of the larynx are atretic; type 2, in which the atresia is infraglottic; and type 3 in which the atresia is glottic. The present case seems to be a type 1 deformity.
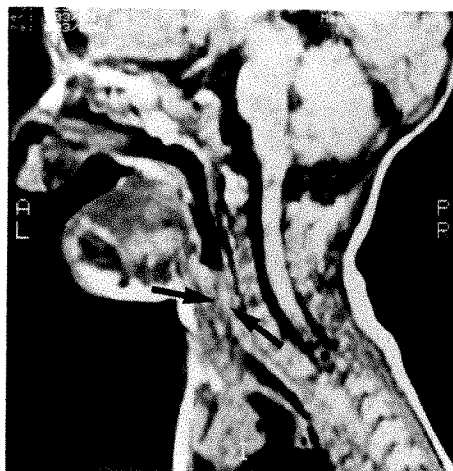
Figure 1. Magnetic resonance image showing glottic and subglottic atresia (**arrows**) of the larynx.

The clinical picture is rather characteristic. During labor, fetal distress is absent, and when born, the infant appears completely normal. Once the cord is clamped, however, the infant develops cyanosis despite respiratory efforts. Severe sternal and intercostal retractions are seen with no air entry into the lung. Intubation attempts are unsuccessful. Without tracheotomy, death occurs shortly after birth. The diagnosis is made by clinical observation and confirmed by immediate laryngoscopy.

Tracheoesophageal (TE) fistula is a commonly associated anomaly. Fox and Cocker (4) described 16 cases of laryngeal atresia in which 5 were associated with TE fistula. TE fistula was not present in our case. One must not confuse a pharyngotracheal duct with a TE fistula. The opening of a pharyngotracheal duct appears in a postcricoid position, whereas a TE fistula is positioned below the cricoid cartilage, most frequently in the region of the tracheal bifurcation (2).

Our patient survived without as yet any obvious neurological defects in spite of asphyxia for approximately 15 min. Possible factors that may have enabled the patient to be free of signs of overt hypoxic brain damage include, first, the ability of newborns to tolerate hypoxia better than an adult due primarily to immature brain tissue with a lower rate of energy metabolism (6). Second, the heart did not stop beating, with the circulation perhaps providing at least some buffering cerebral metabolic acidosis during hypoxia (6).

In conclusion, we describe a newborn infant with congenital laryngeal atresia delivered by cesarean section. Emergency tracheotomy saved the infant. Obvious neurological defects had not developed, when the infant was last seen at the age of 10 months despite 15 min of severe asphyxia.

References

1. Rossi F. De nonullis monstrositatibus in intermis humani corporis partibus observationes. Mem R Accad Torino 1826;30:155.

2. Gatti WM, MacDonald E, Orfei E. Congenital laryngeal atresia. Laryngoscope 1987;97:966–9.

3. Smith II, Bain AD. Congenital atresia of the larynx. Ann Otol Rhinol Laryngol 1965;74:338–49.

4. Fox H, Cocker J. Laryngeal atresia. Arch Dis Child 1964; 39:641–5.

5. Cohen SR. Congenital atresia of the larynx with endolaryngeal surgical correction: a case report. Laryngoscope 1971;81:1607–15.

6. Fisher DE, Paton JB. Resuscitation of the newborn infant. In: Klaus MH, Fanaroff AA, eds. Care of the High-Risk Neonate. Philadelphia: WB Saunders, 1979:23–44.

Anesthetic Management of a Patient with Bullous Pemphigoid

Kamla K. Prasad, MD and Linda Chen, MD

Key Words: COMPLICATIONS, BULLOUS PEMPHIGOID.

Bullous pemphigoid is an autoimmune skin disorder characterized by subepidermal bullae formation involving most commonly the intertriginous areas but also the oropharyngeal, esophageal, and other mucous membranes. Although there is literature describing anesthetic management of epidermolysis bullosa, a disease that pemphigoid resembles, no case reports discussing the anesthetic management of bullous pemphigoid could be found. We report the use of continuous spinal anesthesia for a patient undergoing radical vulvectomy with a history of intraoral and epiglottic bullae.

Case Report

A 49-year-old black female with stage IV vulvar carcinoma was admitted for radical vulvectomy and bilateral femoral and pelvic node dissection. Two months before the scheduled surgery, the patient noted the development of bullous eruptions on her extremities. The patient's past medical history was significant for recurrent phlebitis, possibly related to previous oral contraceptive use, and an old myocardial infarction based on electrocardiogram (ECG) findings; however, her history was negative for collagen vascular or dermatologic disease, significant family history, drug ingestion, or recent viral illness. Examination revealed erythematous lesions with central bullae on the inner thighs, arms, and the plantar surfaces of the feet. Routine laboratory values were within normal limits. Administration of oral prednisone, 40 mg once daily, was empirically started on an outpatient basis, but the number of lesions increased, and they became pruritic.

Because of the failure of low-dose prednisone therapy, a skin biopsy was performed approximately 6 weeks before the scheduled surgery. Biopsy revealed massive subepidermal papillary edema with superficial mononuclear and eosinophilic infiltrates Immunofluorescence showed IgG and C3 at the epidermal junction, consistent with bullous pemphigoid. Based on the pathology of the lesions, the patient was started on therapy more specifically appropriate for pemphigoid: oral prednisone was increased incrementally to 80 mg daily, and azathioprine, 50 mg twice daily, was begun. However, 2 weeks before the scheduled surgery and after 4 weeks of combination prednisone and azathioprine therapy, the patient developed intraoral bullae and complained of difficulty swallowing. Indirect laryngoscopy revealed an epiglottic bulla that was not obstructing her airway. Because of the failure of outpatient oral prednisone therapy, the patient was admitted for high dose intravenous steroid administration and intravenous hydration. Her lesions markedly resolved, and she was discharged on medication that included 80 mg prednisone, twice daily, plus azathioprine, 50 mg twice a day.

On the admission for vulvectomy, physical examination revealed an ulcerated pemphigoid lesion on the lower gums and no intraoral lesions. Pemphigoid lesions at various stages of healing were found on the neck, left axilla, and abdomen. Laboratory tests and chest x-ray were within normal limits. The electrocardiogram showed normal sinus rhythm and evidence of an old inferior wall myocardial infarction. Preoperatively, the patient was taking oral prednisone, 70 mg, and azathioprine, 100 mg daily.

Premedication included morphine sulfate (6 mg IV), scopolamine (0.43 mg IV), and hydrocortisone (100 mg IV). Because the patient denied problems in the recent past with nonallergic adhesive tape, the IV catheter, precordial stethoscope, ECG pads, and blood pressure cuff were applied in the usual manner. Continuous catheter spinal anesthesia was the anesthetic technique selected. The initial injection of 6 mg of 0.2% hyperbaric tetracaine resulted in a T

level of sensory blockade bilaterally. An additional 5 mg of tetracaine was incrementally administered during the operation to maintain a sensory blockade of T_4 to T_6 bilaterally. The patient was awake, comfortable, and breathing spontaneously throughout the 7-hr operation. Intraoperative surgical and anesthetic course was uneventful. Postoperatively, the patient had increased pemphigoid activity with new bullous and erythematous lesions of the face and inframammary area. There were no lesions at the sites of spinal needle puncture, blood pressure cuff placement, or IV cannulation. There were also no lesions at pressure points that had been in contact with the operating room table during surgery. After a benign postoperative course, the patient was discharged on the 5th postoperative day.

Discussion

Bullous pemphigoid, a bullous skin disorder that can affect all age groups, is predominantly a disease that occurs after the fifth decade of life (1,2). The pemphigoid group of diseases are classified among the chronic, nonhereditary blistering skin diseases, as are pemphigus, dermatitis herpetiformis, and erythema multiforme. The pemphigoid group includes bullous pemphigoid, cicatricial pemphigoid, localized scarring pemphigoid (Brunsting–Perry), and herpes gestationis. Although clinical findings within the pemphigoid group may differ, the group shares similar histopathologic and immunopathologic findings. Bullous pemphigoid is characterized by the formation of large, tense bullae arising in either normal appearing or erythematous skin and most commonly involves the intertriginous areas of the arms, thighs, axilla, and lower abdomen, but can also involve oropharyngeal, esophageal, anal, and vaginal mucous membranes. The disease follows a chronic course of exacerbations and remissions.

Histopathologically, bullous pemphigoid is characterized by subepidermal bulla formation, with the intact epidermis forming the roof of the blister and the basal lamina forming the floor. The bullae contain an inflammatory infiltrate of neutrophils, lymphocytes, and eosinophils. The disease is autoimmune in origin. Complement-fixing IgG autoantibodies reactive with the basal lamina of the skin are found in the serum of the majority of cases. Direct immunofluorescence studies reveal IgG and complement components in most skin lesions.

Treatment of bullous pemphigoid usually includes systemic corticosteroids and immunosuppressive agents. Oral prednisone, 50–100 mg daily, is com-

monly used to suppress acute exacerbation whereas combination azathioprine and steroid therapy is used for maintenance. Methotrexate, cyclophosphamide, sulfapyridine, and sulfones (Dapsone) have also been used in therapy.

Anesthetic Management

Whereas there is extensive literature on the anesthetic management of epidermolysis bullosa, a rare hereditary disorder characterized by intraepidermal bullae formation after friction or trauma, no previous case reports on the anesthetic management of bullous pemphigoid could be found, and there was only one report of cicatricial pemphigoid in which severe upper airway obstruction was managed with intubation (3). Because of the similarities between epidermolysis bullosa dystrophica (EBD) and pemphigoid, anesthetic considerations are believed to be the same for both (4), and we cite existing literature on EBD as a guide to management of pemphigoid.

Patients with pemphigoid have special anesthetic requirements. Airway management may be difficult because of preexisting bullae in the oropharynx, and airway instrumentation may cause acute bullae formation with risk of hemorrhage and airway obstruction. Frictional trauma to skin, especially lateral shearing forces, may result in new lesions. Other autoimmune diseases may be associated with pemphigoid and may require management. Electrolyte abnormalities may be present if lesions are widespread. Finally, potential side effects of drug therapy, notably corticosteroids and azathioprine, must be considered. Long-term steroid use, especially in high doses, may result in sodium and fluid retention, hypokalemic alkalosis, gastroduodenal ulceration, hyperglycemia, and impaired wound healing. Azathioprine administration may be complicated by reversible leukopenia and thrombocytopenia, secondary to bone-marrow suppression, and reversible hepatotoxicity with biliary stasis. Both drugs increase the risk of secondary infection.

A regional anesthetic technique was selected in our patient to avoid potential complications of airway manipulation with a mask or endotracheal tube, especially given this patient's history of intraoral and epiglottic lesions. The use of regional anesthesia in the presence of bullous skin disease is controversial (5–7). Some authors argue that regional anesthesia is inappropriate for various reasons: because of the possibility that infected bullae might form at the site of injection; because the effect of prolonged immobilization during somatic and motor blockade

is unknown; and because of the danger of inflicting initially undetected trauma to anesthetized skin. However, ten reported cases of brachial plexus anesthesia on patients with EBD undergoing surgical correction of pseudosyndactyly and flexion contractures revealed no complications (8,9). Several reports of successful, uncomplicated epidural and spinal anesthetics in patients with bullous skin disease have also been reported (10–12). Local infiltration anesthesia is generally contraindicated because of the risk of skin sloughing and bullae formation at the site of injection.

When inhalation anesthetics are used in patients with EBD, intubation is frequently avoided, when possible, to avoid bullae formation in the oropharynx or on the posterior surface of the epiglottis, which may lead to immediate or postoperative supralaryngeal obstruction. However, an anesthetic face mask also poses the risk of severe bullae formation. When a face mask is used, the skin that is likely to come in contact with the mask and the anesthesiologist's fingers may be generously covered with lubricant gel and hydrocortisone ointment, and well lubricated cotton wadding may be placed between face and mask. The need for direct contact between face and anesthesia mask was circumvented in one EBD patient undergoing orthopedic surgery by the use of a clear polyethylene head hood in a spontaneously ventilating patient (13). Halothane, oxygen (O_2), and nitrous oxide were delivered through an inhalation port with pressures within the hood controlled by a variable lumen exhalation port. High flow rates distended the hood, preventing skin contact. No artificial airway was used. In another case, anesthesia was maintained by insufflating anesthetic gases through a fixed delivery tube to the side of the patient's mouth (14).

Spontaneous ventilation ketamine general anesthesia has been used in EBD patients because it allows for minimal manipulation of the airway. Ketamine general anesthesia provided for rapid induction, good analgesia, preservation of airway reflexes, and maintenance of a good airway, all of which serve to minimize trauma to the face and upper airway in EBD patients. In two EBD patients undergoing surgery, one of whom had an extensive 4-hr orthopedic procedure, no supplemental O_2 was given (15,16). In other cases, supplemental O_2 via nasal cannula or by holding a mask near but not in contact with the face was provided (17,18). To minimize the possibility of ketamine-related "emergence delirium" and trauma to sensitive skin and mucosa, benzodiazepine premedicants have often been used.

Despite these concerns about causing severe air-

way trauma in patients with friable mucosa, numerous reports of uncomplicated elective endotracheal intubations in patients with EBD have been reported (5,6,19–21). In many instances, elective intubation has been favored over the potentially traumatic insertion of a tracheal tube as an emergency procedure should airway obstruction occur (6). In one retrospective study, 131 endotracheal intubations in EBD patients were performed without a single case of intraoperative or postoperative airway obstruction. Although six instances of postoperative anesthesia-related facial and intraoral bullae formation have been reported, all of which were minor, there have been no reports of laryngeal or tracheal bullae formation during or after anesthesia (22).

To avoid frictional trauma to the airway in EBD patients, the laryngoscope and endotracheal tube should always be liberally lubricated, and the face and lips are often pretreated with 1% hydrocortisone cream and vaseline gel (21). Trauma may be further minimized by using a warmed, therefore softer, endotracheal tube, by maintaining minimal cuff inflation pressure or avoiding cuff inflation altogether, and by using a Macintosh rather than a Miller laryngoscope blade to minimize trauma to the posterior surface of the epiglottis (20). A tube smaller than usual should be used, and oral intubation is preferred over the nasal route. Oral airways should be avoided (9). The tracheal tube should be secured with a soft cloth bandage rather than with adhesive tape, and care should be taken to ensure that no lateral force is exerted by the tube at the corner of the mouth. Direct laryngoscopy before extubation to evaluate for bullae formation may be considered, although this procedure perhaps unnecessarily induces additional trauma (21). Suction catheters should be well lubricated and suction pressures minimized. Extubation should be gentle, and the patient should be observed postoperatively for stridor. An obstructing bulla may be treated by rupturing the bulla and application of topical steroids (15).

The anesthetic management of EBD requires special precautions to prevent trauma to sensitive skin. In cases where adhesive tape is used to secure the tracheal tube, intravenous cannula, or precordial stethoscope, the skin may peel off, leaving large raw areas with serous drainage. Electrocardiograph leads and precordial stethoscope should be secured with minimal adhesive tape or with a cloth bandage. Blood pressure (BP) cuffs must be well padded. Some authors argue that a BP cuff should be avoided altogether; instead, BP should be monitored by an arterial cannula secured with sutures and not tape. The use of a Doppler monitor or just palpation of the

carotid pulse for BP assessment in EBD patients without significant cardiovascular disease has also been advocated (19). Eyes should be lubricated, not taped shut. It is preferable to avoid premedication and to allow the patient to move and position himself onto the operating room table. Sheets under the patient should be free of creases, and foam padding should be used to protect heels and elbows. A smooth induction of and emergence from anesthesia without struggling will reduce the amount of skin trauma. Supplemental IV corticosteroids should be considered preoperatively and intraoperatively.

In conclusion, bullous pemphigoid, though in many ways similar to EBD, is generally a milder skin disease. In the patient with bullous pemphigoid that we report, regional anesthesia rather than general anesthesia was chosen to prevent oropharyngeal trauma and potential airway obstruction. However, no other precautions were taken to avoid skin or mucous membrane bulla formation, and the patient experienced no significant intraoperative or postoperative exacerbation of her skin disease. Although it is difficult to extrapolate from outcome in one patient, the precautions required in managing patients with epidermolysis bullosa dystrophica may not necessarily be required in patients with bullous pemphigoid.

References

1. Jordan RE. Bullous skin diseases. In: Stein JH, ed. Internal medicine, 1st ed. Boston: Little Brown & Co, 1983:1015–6.
2. Berryhill RE. Skin and bone disorders. In: Katz J, Benumof J, Kadis LB, eds. Anesthesia and uncommon diseases: pathophysiologic and clinical correlation, 2nd ed. WB Saunders Company, Philadelphia, 1981:562–83.
3. Drenger B, Zidenbaum M, Reifen E, Leitersdorf E. Severe upper airway obstruction and difficult intubation in cicatricial pemphigoid. Anaesthesia 1986;41:1029–31.
4. Smith GB, Shribman AJ. Anaesthesia and severe skin disease. Anaesthesia 1984;39:443–55.
5. Reddy ARR, Wong DHW. Epidermolysis bullosa: a review of anaesthetic problems and case reports. Can Anaesth Soc J 1972;19:536–47.
6. Hubbert CH, Adams JG. Anesthetic management of patients with epidermolysis bullosa. South Med J 1977;70:1375–7.
7. Berryhill RE, Benumof JL, Saidman LJ, Smith PC, Plumer MH. Anesthetic management of emergency cesarean section in a patient with epidermolysis bullosa dystrophica polydyspslastica. Anesth Analg 1977;57:281–3.
8. Kaplan R, Strauch B. Regional anesthesia in a child with epidermolysis bullosa. Anesthesiology 1987;67:262–4.
9. Kelly RE, Koff HD, Rothaus KO, Carter DM, Artusio JF. Brachial plexus anesthesia in eight patients with recessive dystrophic epidermolysis bullosa. Anesth Analg 1987;66:1318–20.
10. Spielman FJ, Mann ES. Subarachnoid and epidural anaesthesia for patient with epidermolysis bullosa. Can Anaesth Soc J 1984;31:549–51.
11. Broster T, Placek R, Eggers GWN. Epidermolysis bullosa: anesthetic management for cesarean section. Anesth Analg 1987;66:341–3.
12. Jeyaram C, Torda TA. Anesthetic management of cholecystectomy in a patient with buccal pemphigus. Anesthesiology 1974;40:600–1.
13. Petty WC, Gunther RC. Anesthesia for nonfacial surgery in polydysplastic epidermolysis bullosa (dystrophic). Anesth Analg 1970;49:246–50.
14. Marshall BE. A comment on epidermolysis bullosa and its anaesthetic management for dental operations. Br J Anaesth 1963;35:724–7.
15. Hamann RA, Cohen PJ. Anesthetic management of a patient with epidermolysis bullosa dystrophica. Anesthesiology 1971;34:389–91.
16. LoVerme SR, Oropollo AT. Ketamine anesthesia in dermolytic bullous dermatosis (epidermolysis bullosa). Anesth Analg 1977;56:398–401.
17. Block MS, Gross BD. Epidermolysis bullosa dystrophica recessive: oral surgery and anesthetic considerations. J Oral Maxillofac Surg 1982;40:753–8.
18. Holzman RS, Worthen HM, Johnson KL. Anaesthesia for children with junctional epidermolysis bullosa (letalis). Can J Anaesth 1987;34:395–9.
19. Milne B, Rosales JK. Anesthesia for correction of oesophageal stricture in a patient with recessive epidermolysis bullosa dystrophica: case report. Can Anaesth Soc J 1980;27:169–71.
20. Tomlinson AA. Recessive dystrophic epidermolysis bullosa: the anaesthetic management of a case for major surgery. Anaesthesia 1983;38:485–91.
21. Wright JT. Epidermolysis bullosa: dental and anesthetic management of two cases. Oral Surg 1984;57:155–7.
22. James I, Wark H. Airway management during anesthesia in patients with epidermolysis bullosa dystrophica. Anesthesiology 1982;56:323–6.

Respiratory Responses Associated with Release of Intraoperative Tourniquets

Denis L. Bourke, MD, Marc S. Silberberg, MD, Rafael Ortega, MD, and Marcelle M. Willock, MD

Tourniquets are often used for surgery on the extremities to provide a bloodless surgical field. Tourniquets can, however, cause nerve and other tissue injuries, while inflation of the tourniquet can cause hypertension (1,2), and deflation can cause hypotension (3,4). Decreases in arterial pH and Po_2, and increases in Pco_2 immediately following tourniquet deflation have been documented (5–12). Our study examines the end-tidal CO_2 ($P_{ET}co_2$) changes and the respiratory responses related to acidosis and $P_{ET}co_2$ increases following tourniquet deflation in spontaneously breathing and ventilation-controlled patients during several types of anesthesia.

Methods

With institutional approval we studied 40 ASA physical status I or II patients who were between the ages of 20 and 60 and were undergoing elective knee arthroscopy. We studied consecutive patients until each of four groups included ten subjects. Group IG consisted of patients who were given enflurane nitrous oxide (N_2O) without narcotics for maintenance anesthesia and who were breathing spontaneously at the time of tourniquet deflation. Group NG consisted of patients in whom anesthesia was maintained with fentanyl and N_2O and who were breathing spontaneously at the time of tourniquet deflation. Group SG consisted of patients given spinal anesthesia who

were awake at the time of tourniquet deflation. Group CG consisted of patients given general anesthesia whose ventilation was controlled at the time of tourniquet deflation regardless of anesthetic technique. Otherwise the selection and conduct of anesthesia were determined by the anesthesiologist.

During the 5 min before tourniquet deflation and for the 15 min after tourniquet deflation, we measured tidal volume (V_T), respiratory rate (f), $P_{ET}co_2$, and mixed-expired CO_2. CO_2 measurements were made using a Gould-Godert Capnograph. Ventilation measurements were made with a Med-Science Wedge Spirometer or, in the CG group, with a Dragerwerkag Lubeck Volumeter 3000. Blood pressure, heart rate, and electrocardiogram (ECG) were recorded at 2-min intervals during the observation period.

All measurements were corrected to body temperature pressure standard (BTPS). We estimated total body CO_2 production as 1.10 times the CO_2 elimination observed during the control period based on preliminary study results that showed a 10% decrease in CO_2 elimination following leg tourniquet inflation. Excess CO_2 elimination ($V_{EX}co_2$) was calculated as the total CO_2 eliminated after tourniquet deflation in excess of our estimated total body CO_2 production. The time for CO_2 elimination to return to normal was calculated as the time from tourniquet deflation until CO_2 became equal to estimated CO_2 production.

Two-point CO_2-response curve slopes were calculated for each subject using the baseline $P_{ET}co_2$ and V_E and the mean values of $P_{ET}co_2$ and V_E during the 1 min following each subject's peak $P_{ET}co_2$.

Statistical analysis included analysis of variance, t-tests, and linear regression analysis (13). Statistical significance was set as the probability of a Type I error being less than or equal to 0.05 with corrections for multiple comparisons when appropriate. All values are reported as mean $\pm$ 1 SD unless otherwise noted.

Table 1. Patient Characteristics

Group	n	Height (cm)	Weight (kg)	Age (yr)	Sex (M/F)
IG	10	177 ± 6	73.4 ± 9.2	41 ± 12	7/3
NG	10	176 ± 7	72.6 ± 9.1	43 ± 9	7/3
SG	10	174 ± 5	70.3 ± 8.4	40 ± 10	6/4
CG	10	174 ± 6	68.3 ± 10.2	37 ± 11	5/5

IG = inhalational group; NG = narcotic group; SG = spinal group; CG = controlled ventilation group. Values are expressed as means ± SD.

Table 2. Maximum Changes in Blood Pressure and Heart Rate in the 5 Min following Tourniquet Deflation

Group	n	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart Rate (beats/min)
IG	10	−8 ± 3	−7 ± 5	7 ± 4
NG	10	−6 ± 2	−6 ± 3	7 ± 3
SG	10	−5 ± 3	−7 ± 3	10 ± 5
CG	10	−8 ± 4	−9 ± 3	8 ± 4

IG = inhalation group; NG = narcotic group; SG = spinal group; CG = controlled ventilation group. Values are expressed as means ± SD.

Results

Demographically, all four groups were similar (Table 1). Mean tourniquet inflation time for all patients was 67 ± 30 min with no significant difference among the four groups. Following tourniquet deflation, blood pressures decreased and heart rates increased, but neither change was statistically significant, and there were no significant intergroup differences (Table 2). Two patients in the CG group had several premature ventricular contractions; otherwise, there were no unusual ECG events.

Table 3 shows, for each group, tourniquet inflation times; maximum increases in $P_{ET}CO_2$; times between tourniquet deflation and the maximum increase in $P_{ET}CO_2$; the maximum increase in V_E; the time between tourniquet deflation and maximum increase in V_E; the time between tourniquet deflation and return of $P_{ET}CO_2$ to within 2 mm Hg of the baseline $P_{ET}CO_2$; the time between tourniquet deflation and return of CO_2 elimination to within 10% of the estimated total body CO_2 production; and the CO_2-response curve slopes.

Figures 1 and 2 show, respectively, plots of $P_{ET}CO_2$ and V_E as a function of time after tourniquet deflation. Due to differences in anesthetic technique, baseline $P_{ET}CO_2$ and V_E values were not comparable for all groups. $P_{ET}CO_2$ values for the CG and SG groups were similar to each other but significantly different from $P_{ET}CO_2$ values for both the NG and IG groups, which were similar to each other. Significant baseline differences for V_E occurred only between the SG and IG groups.

Linear least mean squares and regression of $V_{EX}CO_2$ versus tourniquet time (t) was $V_{EX}CO_2$ = (5.7) (t) + 179, with a correlation coefficient of 0.78. Maximum increase in $P_{ET}CO_2$ and maximum increase in V_E (except for the CG group) were also related to tourniquet inflation time but less strongly than $V_{EX}CO_2$.

Discussion

Our results show, as do those of others, a rapid increase in $P_{ET}CO_2$ after tourniquet deflation (10,11). However, our measurements of respiratory responses yielded new information on the responses to tourniquet deflation. Others (10,11) have demonstrated that tourniquet deflation is also associated with a transient metabolic acidosis that would itself affect the ventilatory response. We did not take blood samples and therefore report only the relationships between V_E and $P_{ET}CO_2$.

Despite considerable differences in anesthetic techniques, the ventilatory response of spontaneously breathing patients was brisk and effective in returning $P_{ET}CO_2$ to near baseline in a short time regardless of anesthetic technique. However, in patients in whom ventilation was controlled (Figure 2), $P_{ET}CO_2$ remained above baseline for over 6 min, nearly twice as long as any other group. Further, spontaneous ventilation, regardless of anesthetic technique, prevented the increase in $P_{ET}CO_2$ that followed tourniquet deflation from being as large as it was in patients whose ventilation was controlled. It is surprising that there were no significant differences in these measurements among the anesthetic technique employing spontaneous ventilation. One would have expected that patients lightly premedicated with spinal anesthesia would have responded differently from those breathing spontaneously during a primarily inhalational anesthetic technique.

Calculated excess CO_2 elimination, that is, total CO_2 elimination more than 10% greater than the CO_2 elimination observed before tourniquet deflation, was nearly linearly related to tourniquet inflation time. This relationship was maintained beyond the 30-min period after which aerobic metabolism is presumed to cease during ischemia following inflation of a tourniquet. We assume that rapid combustion of lactate in the tricarboxylic acid cycle produced the CO_2 that maintained the excess CO_2 elimination versus tourniquet time relationship for tourniquet inflation times as long as nearly 3 hr.

Our results indicate that regardless of anesthetic technique, patients with adequate spontaneous ventilation respond to the extra CO_2 load imposed by

Table 3. Tourniquet, CO_2, and Respiratory Data

	IG 10	NG 10	SG 10	CG 10
Tourniquet time (min)	59.4 ± 25.8	74.2 ± 35.1	66.9 ± 22.4	68.7 ± 35.6
Maximum $P_{ET}CO_2$ increase after tourniquet deflation (mm Hg)	5.3 ± 3.7*	4.5 ± 2.3*	7.3 ± 3.9*	11.1 ± 4.1*
Time to maximum $P_{ET}CO_2$ increase after tourniquet deflation (min)	1.9 ± 0.6	1.8 ± 0.3	1.7 ± 0.6	2.7 ± 1.1†
Maximum V_E increase after tourniquet deflation (L/min)	3.09 ± 1.83*	3.60 ± 2.25*	5.12 ± 3.12*	—
Time to maximum V_E increase after tourniquet deflation (min)	2.6 ± 0.8	2.2 ± 0.6	2.3 ± 0.6	—
Time for $P_{ET}CO_2$ to return to baseline (min)	6.0 ± 2.7	4.7 ± 2.3	6.3 ± 2.9	>15†
Time for excess CO_2 elimination to return to 10% of baseline (min)	6.8 ± 1.8	6.0 ± 1.7	4.9 ± 1.5	11.4 ± 1.7*
CO_2-response curve slope (L·min^{-1}·torr^{-1})	0.62 ± 0.43	1.01 ± 1.21	1.46 ± 1.23	—

*Significantly different ($P < 0.05$) from baseline value.
†Significantly different ($P < 0.05$) from values in other groups.
IG = inhalational group; NG = narcotic group; SG = spinal group; CG = controlled ventilation group. Values are expresed as means ± SD.

Figure 1. Changes in end-tidal CO_2 ± SEM after tourniquet deflation for various anesthetic techniques. NG = narcotic group, IG = inhalation group, SG = spinal group, and CG = controlled ventilation group. $n = 10$ for each group. Asterisks indicate values that are significantly different ($P < 0.05$) from values immediately prior to tourniquet deflation.
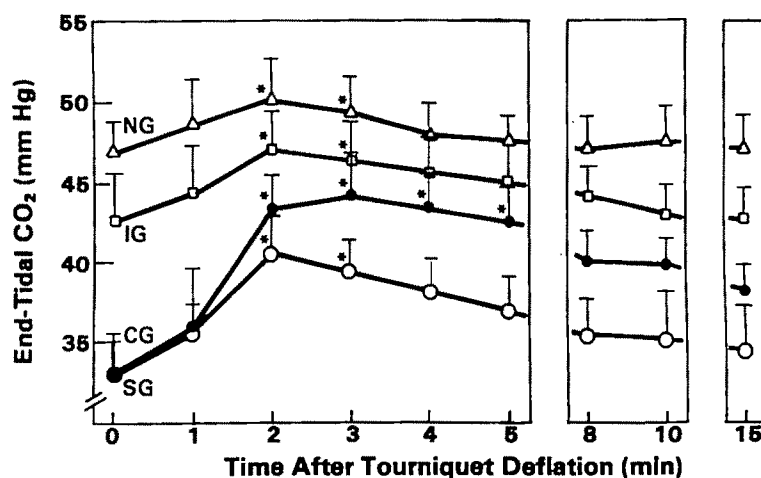
Figure 2. Changes in minute ventilation ± SEM after tourniquet deflation for various anesthetic techniques. SG = spinal group, CG = controlled ventilation group, NG = narcotic group, and IG = inhalation group. $n = 10$ for each group. Asterisks indicate values that are significantly different ($P < 0.05$) from values immediately prior to tourniquet deflation.
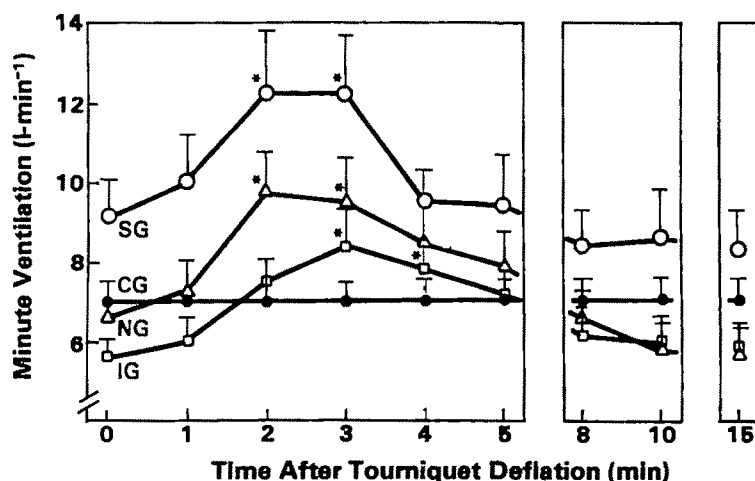
surgical tourniquet deflation vigorously enough to prevent excessive increases in $P_{ET}CO_2$ and will return $P_{ET}CO_2$ to near previous levels within about 3–5 min. However, in order to prevent any increase in $P_{ET}CO_2$, the spontaneous increase in ventilation would have to be further augmented. We calculate from our data that increasing V_E by about 50% for 5 min following tourniquet deflation should prevent $P_{ET}CO_2$ from increasing more than 3–5 mm Hg in most patients. Since tourniquet deflation frequently occurs near the end of a surgical procedure when the anesthetist is lightening anesthesia, and since CO_2 is a potent ventilatory stimulus that may be a sufficiently noxious stimulus to cause patient arousal, increasing V_E at this time might be helpful in preventing patient movement that necessitates additional anesthetics and thus prolongs awakening and recovery.

References

1. Kaufman RD, Walts LF. Tourniquet-induced hypertension. Br J Anaesth 1982;54:333–6.

2. Valli H, Rosenberg PH, Kytta J, Nurminen M. Arterial hypertension associated with the use of a tourniquet with either general or regional anesthesia. Acta Anaesthesiol Scand 1987; 31:279–83.

3. Modig J, Kolstad K, Wigren A. Systemic reactions to tourniquet ischemia. Acta Anaesthesiol Scand 1978;22:609–14.

4. Valli H, Rosenberg PH. Effects of three anaesthesia methods on haemodynamic responses connected with the use of thigh tourniquet in orthopaedic patients. Acta Anaesthesiol Scand 1985;29:142–7.

5. Solonen KA, Tarkkanen L, Narvanen S, Gordin R. Metabolic changes in the upper limb during tourniquet ischaemia; a clinical study. Acta Orthop Scand 1968;39:20–32.

6. Shaw Wilgis EF. Observations on the effects of tourniquet ischemia. J Bone Joint Surg 1971;53A:1343–6.

7. Dery R, Pelletier J, Jacques A, et al. Metabolic changes induced in the limb during tourniquet ischaemia. Can Anaesth Soc J 1965;12:367–78.

8. Klenerman L, Biswas M, Hulands GH, Rhodes AM. Systemic and local effects of the application of tourniquet. J Bone Joint Surg 1980;62B:385–8.

9. Larsson J, Bergstrom J. Electrolyte changes in muscle tissue and plasma in tourniquet-ischemia. Acta Chir Scand 1978; 144:670–73.

10. Patel A, Choi C, Giuffrida JG. Changes in end tidal CO_2 and arterial blood gas levels after release of tourniquet. South Med J 1987;80:213–6.

11. Lynn AM, Fischer T, Brandford HG, Pendergrass TW. Systemic responses to tourniquet release in children. Anesth Analg 1986;65:865–72.

12. Knill RL, Clement JL. Ventilatory responses to acute metabolic acidemia in humans awake, sedated, and anesthetized with halothane. Anesthesiology 1985;62:745–53.

13. Snedecor GW, Cochran WG. Statistical Methods. Ames, Iowa: Iowa State University Press, 1980.

Transient Left Bundle Branch Block following Lidocaine

Thomas M. Tagliente MD, PhD and Salem Jayagopal, MD

Key Words: HEART, BLOCK—left bundle branch. ANESTHETICS, LOCAL—lidocaine.

The sudden occurrence of left bundle branch block (LBBB) during anesthesia and surgery is infrequent. It is generally thought to be associated with significant heart disease, and its sudden appearance may indicate the presence of an acute myocardial infarction. The diagnosis of myocardial infarction by electrocardiogram (ECG) criteria becomes more difficult in the presence of LBBB, an important consideration during anesthesia, when symptomatic diagnosis of infarction and ischemia is obviated. We report here the occurrence of a transient LBBB, which appeared before the induction of anesthesia and which we believe may have been precipitated by the administration of intravenous lidocaine.

Case Report

A 58-year-old, 72-kg, woman presented for a radical hysterectomy and pelvic and para-aortic lymphadenectomy for stage IIB cervical carcinoma. The patient had been treated with several courses of chemotherapy (bleomycin, vincristine, cisplatin, and mitomycin) before surgery. Past medical history was otherwise significant only for a 20 pack/year smoking history. She denied any history of hypertension, heart disease, diabetes, or rheumatic fever. Anesthetic history included several uneventful general anesthetics for minor surgical procedures. She was presently taking no medication and had no known medication allergies. The physical examination was unremarkable. The patient had received a total dose of 30 units of bleomycin, and pulmonary function tests were normal. The hematocrit was 34.7%. Blood

chemistries were all within normal limits, as were the chest x-ray and resting electrocardiogram (ECG). The blood pressure ranged from 120–130/80–90 mm Hg and the heart rate was 80–90 beats/min.

The patient was premedicated with 7.5 mg of oral diazepam 1 hr prior to her arrival in the operating room. In the operating room, an ECG (Lead II), blood pressure cuff, and pulse oximeter were applied. Direct arterial and central venous pressure monitoring was to be initiated after induction. The ECG monitor revealed a normal sinus rhythm with a normal QRS complex. The blood pressure was 130/80 mm Hg and the heart rate was 80 beats/min. In preparation for induction, the patient was preoxygenated and a defasciculating dose of pancuronium (1 mg) and 50 μg of fentanyl were administered. This was followed by an 80 mg IV dose of lidocaine. Approximately 1 min later, the QRS complexes on the ECG became markedly widened and consistent with a LBBB pattern. The blood pressure and heart rate had not changed appreciably (120/80 mm Hg and 85 beats/min). The oxygen saturation was 99%. The patient appeared comfortable and denied chest discomfort and shortness of breath. A 12-lead ECG was obtained which demonstrated a sinus rhythm at a rate of 85 and a prolonged QRS duration in a LBBB pattern. The LBBB spontaneously resolved during the recording of the 12-lead ECG, approximately 10 min after the lidocaine had been administered. The surgical procedure was postponed and the patient was observed for 48 hr with no recurrence of the LBBB. Blood levels of cardiac enzymes were negative for myocardial infarction, and the patient remained asymptomatic.

Subsequent evaluation of the patient included a normal gated blood pool scan with an ejection fraction of 49% and normal wall motion. A 24-hr Holter monitor revealed only occasional episodes of sinus bradycardia and tachycardia. A stress test was significant for the appearance of a LBBB after 4 min of exercise at a heart rate of 160 beats/min, which reverted back to normal conduction when the heart rate decreased to 105 beats/min. The patient was asymptomatic except for fatigue during the LBBB. A

diagnosis of exercise-induced or rate-related LBBB was made. The cardiology consultant recommended beta-blockade with propranolol prior to surgery. The patient subsequently underwent the surgical procedure without incident.

Discussion

Transient LBBB during anesthesia has been infrequently reported. In one report, the appearance of an intermittent LBBB in a patient with no known history of heart disease was attributed to lithium therapy (1), while intraoperative hypertension and probable ischemia may have accounted for its occurrence in another patient (2). A third report described a patient who had an intermittent LBBB during anesthesia and who was subsequently found to oscillate spontaneously between normal conduction and LBBB in the absence of any symptoms or hemodynamic changes (3). Rorie et al. (4) reported a case in which a transient LBBB appeared in a patient when the heart rate increased to 120 beats/min following the administration of atropine. This patient had a history and ECG changes of an old anterior wall myocardial infarction.

The incidence, etiology, and significance of rate-related LBBB remains obscure. Vasey et al. (5) reported its presence in 28 of 2584 (1.1%) consecutive patients in whom stress testing and coronary angiography were performed. Their series included asymptomatic patients undergoing screening exercise stress tests. Seven of ten patients with classical angina pectoris and rate-related LBBB had significant coronary artery disease, while 12 of 13 patients with atypical chest pain and rate-related LBBB had normal coronary arteriograms. Heinsimer et al. (7) followed 15 patients with rate-related LBBB for an average of 6.6 years. Permanent LBBB developed in eight patients, seven of whom had underlying coronary artery disease. The eighth patient had a cardiomyopathy. None developed a high grade A-V block or required pacing. Four of the patients in the series died during the follow-up period, one of a documented myocardial infarction. Three died suddenly, presumably of cardiac causes.

In the present case, a transient LBBB developed at a heart rate of 85 beats/min in a patient who was subsequently shown to develop it at a rate of 160 beats/min. The close temporal proximity between the appearance of the LBBB and the administration of lidocaine led us initially to suspect this as the provoking factor in the appearance of the LBBB. The central nervous system and cardiovascular toxicity of local anesthetics are well known and have been recently

reviewed (8,9). There have been, however, several reports of adverse effects of lidocaine on cardiac conduction after normal doses of intravenous lidocaine. These have included the appearance of type II second-degree heart block (10), asystole (11), and complete heart block in an infant (12). Recent studies have also demonstrated effects of local anesthetics on intraventricular conduction. High doses of lidocaine and bupivicaine delay conduction between Purkinje fibers and ventricular muscle in the rabbit (13), eventually leading to conduction block. In canine heart (14) and humans (15), local anesthetics produce a rate-dependent increase in intraventricular conduction. These findings are consistent with a presumed mechanism of action of local anesthetics—that is, a use-dependent blockade of sodium channels in nerve membranes. This theory speculates that access of local anesthetics to the binding site within the sodium channel, which is the presumed site of action of local anesthetics, is greater when the channels are in the open state associated with depolarization of the membrane during action potential transmission. Thus, the more frequent action potentials are, the more often the sodium channels are open and, therefore, susceptible to the effects of local anesthetics. Rate-related LBBB has been attributed to the effects of increasing heart rate on the refractory period of the left bundle branch (17). We propose that in our patient an abnormality in intraventricular conduction, which produced a rate-related LBBB at high heart rates, was exacerbated by the administration of lidocaine such that the LBBB appeared at a rate which previously supported normal conduction. This occurred after a normal dose of lidocaine. Although it is possible that the rapid IV bolus may have resulted in transiently high levels of lidocaine, the absence of any other symptoms of local anesthetic toxicity make this unlikely. We are also unaware of any reported association between fentanyl or pancuronium and the occurrence of LBBB. Additionally, the small doses of the drugs that were used makes either of them unlikely as the precipitating factor in this case.

All of the antineoplastic drugs which this patient received have been reported to have some degree of cardiotoxicity (18). However, cardiac toxicity is not a prominent toxic effect of any of the agents that this patient received. In addition, the chemotherapy regimen had been completed three weeks before the original presentation for surgery. While it is possible to speculate that the cardiotoxicity of one or a combination of these drugs may have been responsible for the underlying conduction disturbance, the fact that these drugs were last administered three weeks earlier makes it highly unlikely that any of them

could have been the proximate cause of the transient LBBB we observed.

In conclusion, we present a case in which we believe the administration of lidocaine was associated with the appearance of a transient LBBB. To our knowledge, this has not previously been reported with the use of local anesthetics. We would also like to point out that rate-related LBBB is a possible etiology for the appearance of a transient LBBB perioperatively. Since this condition has been associated with underlying heart disease in a significant number of patients, its appearance in a patient not previously suspected of having underlying heart disease probably warrants delay of the surgical procedure, if possible, for further evaluation of the patient's cardiac status.

References

1. Azar I, Turndorf H. Paroxismal left bundle branch block during nitrous oxide anesthesia in a patient on lithium carbonate. Anesth Analg 1977;56:868–70.

2. Pratilla MG, Pratilas V, Dimich I. Transient left bundle branch block during anesthesia. Anesthesiology 1979;51:461–3.

3. Edleman JD, Hurlbert BJ. Intermittent left bundle branch block during anesthesia. Anesth Analg 1980;59:628–30.

4. Rorie DK, Muldoon SM, Krabil DR. Transient left bundle branch block occurring during anesthesia. Anesth Analg 1972; 51:633–7.

5. Vasey C, O'Donnell J, Morris S, McHenry P. Exercise-induced left bundle branch block and its relation to coronary artery disease. Am J Cardiol 1985;56:892–5.

6. Wayne VS, Bishop RL, Cook L, Spodick DH. Exercise-induced bundle branch block. Am J Cardiol 1983;52:283–6.

7. Heinsimer JA, Irwin JM, Basnight LL. Influence of underlying coronary artery disease on the natural history and prognosis of exercise-induced left bundle branch block. Am J Cardiol 1987; 60:1065–7.

8. Covino BG. Toxicity and systemic effects of local anesthetic agents. In: Strichartz GR, ed. Handbook of Experimental Pharmacology. Vol. 81, Local Anesthetics. Berlin: Springer Verlag, 1987:187–212.

9. Reynolds F. Adverse effects of local anesthetics. Br J Anaesth 1987;59:78–95.

10. Hilleman DE, Mohiuddin SM, Destache CJ. Lidocaine-induced second degree Mobitz type II heart block. Drug Intell Clin Pharm 1985;19:669–73.

11. Applebaum D, Halperin E. Asystole following a conventional dose of lidocaine. Am J Emerg Med 1986;4:143–5.

12. Garner L, Stirt JA, Finholt DA. Heart block after intravenous lidocaine in an infant. Can Anaesth Soc J 1985;4:425–8.

13. Moller RA, Covino BG. Cardiac electrophysiological effects of lidocaine and bupivacaine. Anesth Analg 1988;67:107–14.

14. Nattel S. Interval-dependent effects of lidocaine on conduction in canine cardiac Purkinje fibers: Experimental observations and theoretical analysis. J Pharmacol Exp Ther 1987;241:275–81.

15. Morady F, Dicarlo LA, Baerman JM, Krol RB. Rate dependent effects of intravenous lidocaine, procainamide and amiodarone on intraventricular conduction. J Am Coll Cardiol 1985;6:179–85.

16. Gintant GA, Hoffman BF. The role of local anesthetic effects in the actions of antiarrhythmic drugs. In: Strichartz GR, ed. Handbook of Experimental Pharmacology. Vol. 81, Local Anesthetics. Berlin: Springer Verlag, 1987:213–51.

17. Denes P, Wu D, Dhingra RC, Amat-y-Leon F, et al. Electrophysiological observations in patients with rate-dependent bundle branch block. Circulation 1975;51:244–50.

18. Calabresi P, Parks RE jr. Chemotherapy of neoplastic diseases. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The Pharmacological Basis of Therapeutics. New York: Macmillan Pub Co, 1985:1240–1306.

Letters to the Editor

Endotracheal Tube Extension for Endobronchial Intubation

Key Words: INTUBATION, ENDOBRONCHIAL.
ANESTHETIC TECHNIQUES, ENDOBRONCHIAL.

To the Editor:

Patients occasionally present for surgery requiring endobronchial intubation under circumstances in which surgical requirements obviate the use of a double lumen endotracheal tube. In certain instances, an ordinary endotracheal tube may not be long enough to safely accomplish endobronchial intubation. We describe such a situation requiring extension of an ordinary endotracheal tube and the technique by which this was accomplished.

A 31-year-old, 56.4-kg, 147.5-cm female patient presented for sleeve resection of a right mainstem endobronchial tumor. The surgeon stated that he could not work around a left sided double-lumen endotracheal tube in this patient. Left mainstem endobronchial intubation, therefore, was planned with use of an ordinary endotracheal tube. During fiberoptic bronscopy before surgical incision,

the surgeon expressed concern that our ordinary 33-cm endotracheal tube might not be long enough to intubate the left mainstem bronchus. In our department, a longer endotracheal tube was not available in a size appropriate for endobronchial intubation in this patient. This problem was circumvented by cutting a 9.0-mm endotracheal tube 12 cm from its proximal end and placing it over a 6.5-mm endotrachial tube of which the 15-mm adaptor had been removed. The tubes fitted snugly together with an air tight seal; however, for added security, the tubes were sutured together with use of 2.0 silk sutures (Figures 1 and 2). During left mainstem endobronchial intubation, the junction of the two tubes was deep in the patient's mouth; an ordinary 6.5-mm endotracheal tube would have been of insufficient length to safely intubate the left mainstem brochus.

Holzman (1) recently described the extension of an endotracheal tube using a modified 15-mm adaptor to connect the two segments of his extended tube. We believe that our method provides a more secure attachment of endotracheal tube segments and lessens the possibility of intraoperative disconnection.

Cordell L. Bragg, MD
Georgene R. Vukelich, CRNA
Department of Surgery
Anesthesia Section
USAF Medical Center Keesler
Keesler Air Force Base, MS 39534

Figure 1. Extended endotracheal tube compared with an ordinary endotracheal tube. The distal section of the extended tube is chosen in a size appropriate for the patient. The size of the proximal section is selected for a snug fit over the distal section.
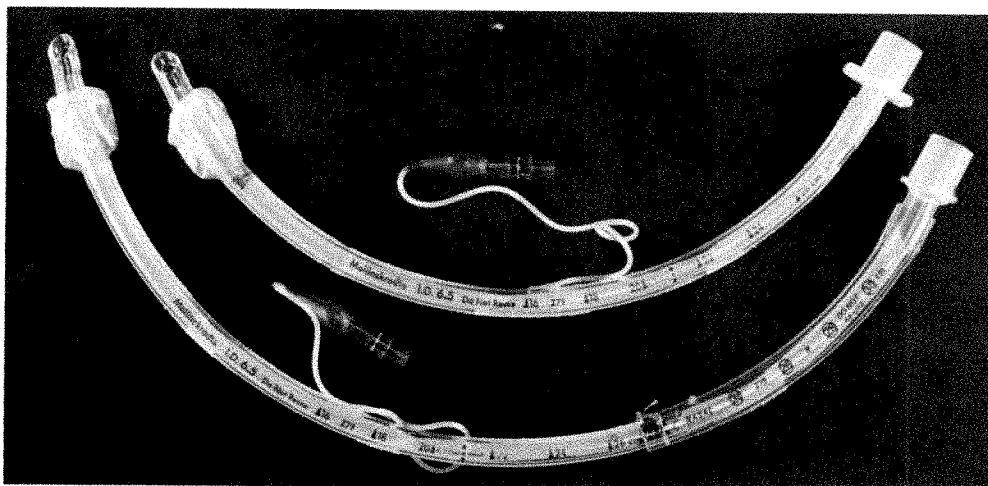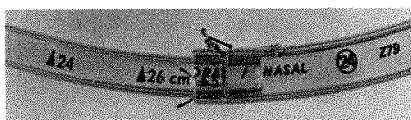
Figure 2. Attachment of the proximal and distal sections of the extended endotracheal tube. The fit is snug and airtight. Suture guards against accidental detachment.

Reference

1. Holzman RS. A tracheal tube extension for emergency tracheal reanastomosis. Anesthesiology 1989;70:170–1.

The Effect of Fentanyl on Basal and Stimulated Plasma Levels of Atrial Natriuretic Peptide

Key Words: ANESTHETICS, INTRAVENOUS— fentanyl. POLYPEPTIDES, ATRIAL NATRIURETIC.

To the Editor:

Hoffman et al. (1) demonstrate that in rats fentanyl does not stimulate atrial natriuretic peptide (ANP) release and does not alter the normal response of plasma ANP level to volume loading. As the authors state, their findings are in contrast to the increase in plasma ANP in rats given morphine (2). Likewise, fentanyl increased ANP levels in another study with rats (3). However, findings similar to those reported by Hoffman et al. were made in a recent study of patients undergoing coronary artery bypass grafting (CABG) with high-dose fentanyl anesthesia (4). Induction of anesthesia with fentanyl did not increase plasma ANP level, but volume loading with 10 mL/kg of body weight of isotonic saline solution and leg raising increased plasma ANP during the subsequent course of anesthesia. As in the study by Hoffman et al., the changes in plasma ANP were related to the changes in cardiac filling pressures in these patients having CABG procedures. It seems that under carefully controlled conditions, i.e. ventilation to normocarbia for instance (1,4), fentanyl does not increase plasma ANP level. Opioid analogues also fail to increase basal plasma level of ANP in conscious healthy volunteers (5). Therefore, although there exist contradictory data, it seems likely that opiate receptors are not involved in ANP release. Atrial distension seems to be the major determinant of ANP release also in anesthetized subjects, at least in patients under high-dose opioid anesthesia.

Markku Hynynen, MD
Department of Anaesthesia
Helsinki University Central Hospital
Helsinki, Finland

References

1. Hoffman WE, Phillips MI, Kimura B. Plasma atrial natriuretic polypeptide and angiotensin II in rats during anesthesia and volume loading. Anesth Analg 1989;68:40–5.

2. Gutkowska J, Horky K, Schiffrin EL, et al. Atrial natriuretic factor: radioimmunoassay and effects on adrenal and pituitary glands. Fed Proc 1986;45:2101–5.

3. Vollmar AM, Arendt RM, Schultz R. The effect of opioids on rat plasma atrial natriuretic peptide. Eur J Pharmacol 1987;143:315–21.

4. Hynynen M, Tikkanen I, Salmenperä M, Heinonen J, Fyhrquist F. Plasma atrial natriuretic peptide concentrations during induction of anesthesia and acute volume loading in patients undergoing cardiac surgery. J Cardiothorac Anesth 1987;1:401–7.

5. Borges F, Anderson JV, Volta C, et al. Opioid peptides do not modulate atrial natriuretic peptide or aldosterone release under basal conditions in man. J Endocrinol 1988;116:313–7.

In Response:

We concur with the conclusions of Dr. Hynynen that under conditions in which ventilation is monitored or controlled, plasma atrial natriuretic peptide (ANP) concentrations do not change during fentanyl administration. It is apparent from previous studies (1–3) that cardiac filling pressure and, more specifically, atrial distension are the primary stimulus for ANP release in both the unanesthetized and fentanyl-anesthetized subject. The mechanism by which morphine or fentanyl may increase plasma ANP in non-ventilated unparalyzed rats is uncertain. One possible mechanism is the change in $Paco_2$ or oxygen delivery associated with hypoventilation. Inadequate ventilation may also be associated with a stress-related hypertensive response which has previously been shown to increase plasma ANP (4). We conclude that control of ventilation is appropriate when testing opioids which may limit normal ventilation.

William E. Hoffman, PhD
Department of Anesthesiology
Michael Reese Hospital and Medical Center
Lake Shore Drive at 31st St.
Chicago, IL 60616

References

1 Hoffman WE, Phillips MI, Kimura B. Plasma atrial natriuretic polypeptide and angiotensin II in rats during anesthesia and volume loading. Anesth Analg 1989;68:40–5.

2 Hynynen M, Tikkanen I, Salmenpera M, Heinonen J, Fyhrquist F. Plasma atrial natriuretic peptide concentrations during induction of anesthesia and acute volume loading in patients undergoing cardiac surgery. J Cardiothorac Anesth 1987;1:401–7.

3 Borges F, Anderson JV, Volta C, et al. Opioid peptides do not modulate atrial natriuretic peptide or aldosterone release under basal conditions in man. J Endocrinol 1988;116:313–7.

4 Imada T, Takayanagi R, Inagami T. Changes in the content of atrial natriuretic factor with the progression of hypertension in spontaneously hypertensive rats. Biochem Biophys Res Commun 1985;133:759–65.

Tourniquet Use and Intraoperative Hypothermia

Key Words: EQUIPMENT, TOURNIQUETS— hypothermia. TEMPERATURE, BODY—tourniquet hypothermia.

To the Editor:

Arm or leg tourniquets have not been mentioned as possible causes of intraoperative hypothermia. We measured esophageal temperatures in 20 patients during knee sur-
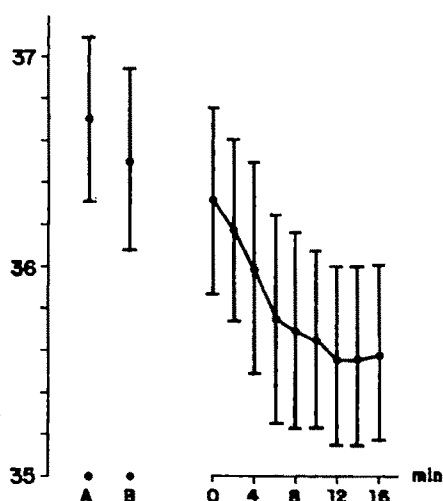
Figure 1. Esophageal temperature (mean ± SD) during general anesthesia for knee surgery in 20 patients. A = Immediately after induction; B = tourniquet inflated; O = tourniquet deflated.

gery under general anesthesia (1). Room temperature was kept at 20°C and ambient humidity at 73% to 81%. The temperature probe was placed at the inferior portion of the esophagus. After tourniquet deflation anesthesia was maintained at a stable level, the rate of intravenous infusion was constant (and minimal), and the patients were covered by surgical drapes. The esophageal temperature decreased 0.33°C (mean) before tourniquet deflation and a further 0.78°C (mean) in the 12 min after deflation, thereafter remaining stable (Figure 1). The following explanations are suggested for the observed decrease in temperature: 1) the cooling effect of blood from the ischemic extremity reaching the systemic circulation; 2) cooling of systemic blood perfusing the hypothermic limb; and 3) reactive hyperemia in the involved extremity with cutaneous hyperemia leading to increased transcutaneous loss of heat. This fortuitous observation should be further studied, because the dangers of inadvertent body hypothermia are well known.

Almiro dos Reis Júnior, MD
Hospital Osvaldo Cruz
Rua João Julião – 331
01323—São Paulo, S.P., Brazil

Reference

1. Reis Júnior, A dos. Temperatura esofagiana e garroteamento de membro inferior. Rev Bras Anest 1989;38:(in press).

Difficult Laryngoscopy and Diabetes Mellitus

Key Words: INTUBATION, TRACHEAL—diabetes and COMPLICATIONS, DIABETES MELLITUS. METABOLISM, DIABETES MELLITUS.

To the Editor:

Like the authors, we too were surprised by the extremely high incidence (32%) of difficult laryngoscopy in diabetic renal transplant patients reported by Hogan et al. (1). They suggested that "stiff joint syndrome," a condition occasionally seen in type I insulin-dependent diabetics, may have been a major cause of this finding. Because their results were so striking, we investigated the incidence of difficult laryngoscopy and intubation in similar patients at our institution.

From January 1986 to December 1988, 68 diabetic and 108 nondiabetic adult patients underwent renal transplant for chronic renal failure. Causes and proportions of chronic renal failure in our patients were similar to those of the previous study (1). The incidence of difficult laryngoscopy and intubation was determined by cross-linkage of our renal transplant and anesthesia data bases. Only 1 (1.5%) of the 68 diabetic patients was judged to be difficult to intubate. There was no difficult intubation in the 108 nondiabetic patients. These findings preclude further analysis of transplant subgroups (cadaveric versus living donor) or demographic and laboratory differences.

Why the marked discrepancy in results? Difficult laryngoscopy and intubation at our institution is a judgment made by our staff anesthesiologists and is similar, but probably not identical, to that used by Hogan et al. To ascertain the influence of any differences in criteria for difficult intubation on our results, we evaluated our institution's overall incidence of difficult intubation during the same time span. Of 89,380 intubations, 568 (0.6%) were judged to be difficult. This rate is similar to the overall norm of 0.5% reported by Hogan et al. Another confounding variable may have been the age of our patients. All of our patients were adults; we are unable to discern how many children were included in the study of Hogan et al. Hogan et al. did not, however, find age to be a predictor of difficult laryngoscopy.

Based on our findings, we are unable to corroborate their report of very strong association between difficult laryngoscopy in diabetic but not nondiabetic renal transplant recipients.

Mary E. Warner, MD
Mark A. Warner, MD
Bradly J. Narr, MD
Department of Anesthesiology
Mayo Clinic and Mayo Medical School
Rochester, MN 55905

Reference

1. Hogan K, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988;67:1162-5.

In Response:

We commend the efforts of Warner et al. in reviewing their experience with laryngoscopy and kidney transplantation from January 1986 to December 1988. Our experience with 247 patients from January 1988 to May 1989 is summarized in Table 1.

A few observations are perhaps warranted. First, the problem of difficult laryngoscopy in renal transplant recipients has not gone away at our institution. Second, diabetes mellitus remains a predictor of difficult laryngoscopy.

Table 1. Routine versus Difficult Laryngoscopy

Operation	Vocal Cords Seen	Vocal Cords Not Seen	Other Difficult*	Difficult/ Routine	% Difficult
Cadaver renal transplant					
Diabetic	24	5	4	9/33	27
Nondiabetic	73	10	2	12/85	14
Living donor transplant					
Diabetic	13	4		4/17	24
Nondiabetic	68	5	1	6/74	8
Pancreas and renal transplant (diabetic)	31	6	1	7/38	14
Total	209	30	8		

*Unspecified difficult laryngoscopy in record, e.g., "anterior larynx."

Third, nondiabetic kidney recipients appear to be at increased risk in comparison with our previous report (1).

Since that investigation, we no longer perform isolated pancreas transplants, living donor transplants for diabetic renal recipients have halved, and living donor transplants for nondiabetic recipients have doubled. These demographic changes, coupled with heightened awareness of potential airway complications on the part of our anesthesiologists, may explain differences between the sampled intervals. The direction and magnitude of these effects can only be matters for speculation with existing data.

It is even more difficult to reconcile the different incidences reported between institutions on the basis of chart review. Because the scored variable is explicit (i.e., can the vocal cords be seen or not?), judgmental differences are unlikely to play a significant role, but cannot be ruled out with certitude. The findings of Warner et al. reinforce our conviction that a prospective investigation, incorporating data from more than a single institution, is required before the association of diabetes mellitus, kidney transplantation, and difficult laryngoscopy may be considered proven or refuted.

Kirk J. Hogan, MD
Deborah Rusy, BS
Scott R. Springman, MD
Department of Anesthesiology
University of WI
Madison, WI 53792

Reference

1. Hogan KJ, Rusy D, Springman SR. Difficult laryngoscopy and diabetes mellitus. Anesth Analg 1988;67:1162-5.

Interpleural Anesthesia for Extracorporeal Shock Wave Lithotripsy

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural.

To the Editor:

Strømskag and Steen (1) reported disappointing results using interpleural regional anesthesia for extracorporeal shock wave lithotripsy (ESWL). Before interpleural anesthesia is abandoned for ESWL, however, additional information is needed about certain aspects of the technique used in this report. For example, was the patient in the horizontal or head-down position during and after the local anesthetic was injected? How was the patient positioned during the block—was he or she horizontal or tilted head down? Which intercostal space was used for insertion of the interpleural catheter? Was the patient maintained in the lateral position after injection of local anesthetic, and, if so, for how long? What was the interval between the injection of local anesthetic and the beginning of the ESWL in the two groups?

Adequate analgesia for ESWL requires blockade to the level of the sixth thoracic dermatome (2). A technique using multiple intercostal blocks with skin infiltration of local anesthetics provides adequate analgesia (3). Three different sites of action appear to be involved when local anesthetics are injected into the pleural space: 1) diffusion of the local anesthetic from the pleural space through the parietal pleura and the innermost intercostal muscles resulting in multiple unilateral intercostal nerve blocks; 2) diffusion of the local anesthetic from the pleural space through the most medial portion of the parietal pleura to block the cervical and thoracic portions of the sympathetic trunk and splanchnic nerves; and 3) diffusion of the local anesthetic to the ipsilateral brachial plexus (4–6).

It is important to stress that the position of the patient after the injection of local anesthetic into the pleural space determines in large part the nature and extent of the resulting blockade. A profound unilateral blockade of the cervical and superior thoracic segments of the sympathetic chain can be produced by placing the patient in the lateral decubitus position with the affected side up and the head down 20° for 20–30 min after the injection of local anesthetic. Incomplete blockade of the brachial plexus, as demonstrated by hypesthesia in the C5-T1 dermatomes and motor weakness of the shoulder, arm, and forearm may also result when the patient is positioned in this manner. Injection of 30 mL of 0.5% bupivacaine appears to provide a sufficient volume and concentration resulting in safe plasma levels of local anesthetic (7).

In contrast to the above positioning, we have produced excellent surgical anesthesia for unilateral breast tumor resection by placing the patient in the lateral decubitus position with the affected side down and the head down 20° after the injection of local anesthetic. This position, when maintained for 20–30 min after injection, produces a unilateral blockade of the intercostal nerves from T1 to T9 with complete skin anesthesia and no clinical signs of blockade of the sympathetic chain or the brachial plexus. Although 30 mL of 2% lidocaine provided inadequate surgical anesthesia, injection of 30 mL of 0.5% bupivacaine is successful.

The contrast between these two positions and the two drugs leads us to recommend that Strømskag and Steen consider repeating their study with these technical considerations in mind.

Finn Reiestad, MD
Department of Anesthesiology
University of Colorado Health Sciences Center
4200 E. Ninth Avenue
Denver, CO 80262

William B. McIlvaine, MD, CM, FRCPC
Department of Anesthesiology
The Children's Hospital
1056 E. 19th Avenue
Denver, CO 80218

References

1. Strømskag KE, Steen PA. Comparison of interpleural and epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1988;67:1181–3.

2. Duvall JO, Griffith DP. Epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1985;64:544–6.

3. Milhotra V, Long CW, Meister MJ. Intercostal blocks with local infiltration anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1987;66:85–8.

4. Rocco A, Reiestad F, Gudman J, McKay W. Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. Reg Anaesth 1987;12:10–14.

5. Duranni Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. Anesth Analg 1988;67:479–81.

6. Sihota MK, Holmblad BR. Horner's syndrome after intrapleural anesthesia with bupivacaine for postherpetic neuralgia. Acta Anaesthesiol Scand 1988;32:593–4.

7. Seltzer JL, Larijani GE. Intrapleural bupivacaine: A kinetic and dynamic evaluation. Anesthesiology 1987;67:798–800.

In Response:

The patients in our study (1) were in the horizontal position when the local anesthetic was injected and were kept horizontal until the extracorporeal shock wave lithotripsy (ESWL) treatment started 20 min later. The interpleural catheter was introduced in the seventh intercostal space, and the patients were turned to the supine position 5 min after the injection of the local anesthetic.

Therefore, both the introduction of the interpleural catheter and the patient position were done according to the method recommended by Reiestad and Strømskag.

Our study showed that the original interpleural technique was inadequate for ESWL. Reiestad and McIlvaine point out possible modifications of the technique. For institutions in which ESWL still requires anesthesia, this could be pursued. With our new ESWL equipment, anesthesia is no longer required.

Kjell Erik Strømskag, MD
Department of Anesthesiology
Molde Hospital
N-6400 Molde
Norway

Petter Andreas Steen, MD, PhD
Department of Anesthesiology
Ullevål Hospital
0407 Oslo 4
Norway

Reference

1. Strømskag KE, Steen PA. Comparison of interpleural and epidural anesthesia for extracorporeal shock wave lithotripsy. Anesth Analg 1988;67:1181–3.

Oral Reinforced Endotracheal Tube Crushed and Perforated from Biting

Key Words: EQUIPMENT, TUBES—endotracheal, reinforced.

To the Editor:

A recent occurrence at our institution demonstrated that oral placed reinforced endotracheal tubes (RETTs) in the semiconscious, nonparalyzed patient can be easily damaged. This case involved a 10-year-old 31-kg female patient who underwent a C1–3 laminectomy and excision of a recurrent medulloblastoma. The 5.5-mm (internal diameter) cuffed RETT (manufactured by Bivona, Inc., Gary, IN) used during the 6-hr procedure was left in place postoperatively for controlled ventilation.

On arrival in the intensive care unit, the patient was initially quiet but became agitated shortly after connection to the ventilator. She was moving her head, gagging, and chewing on the RETT. This activity ended shortly after IV sedation had been given.
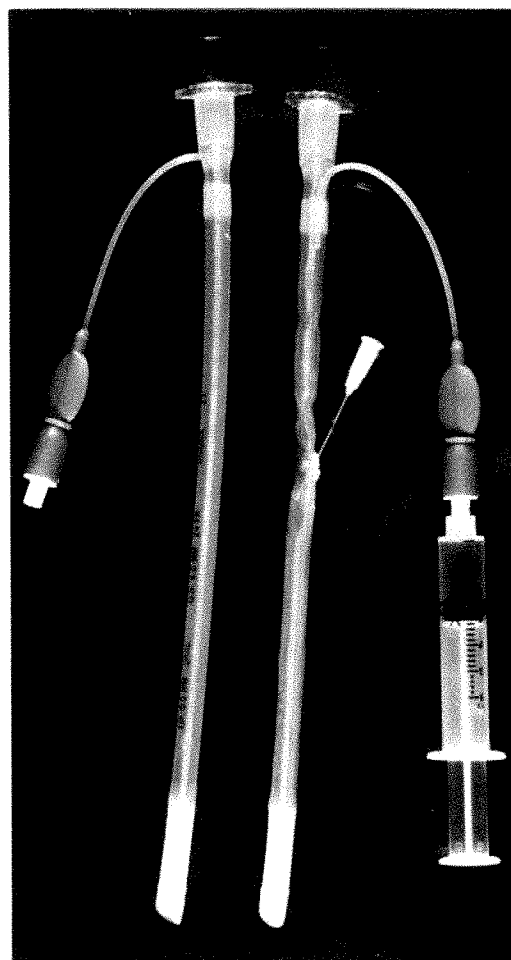

Figure 1. Undamaged reinforced endotracheal tube at left with damaged tube shown at right. The tube at right has a 21-gauge needle inserted to illustrate the laceration that occurred in the silicone portion; the wire reinforcement remained intact.

At the time the patient started her tube-chewing, the nursing staff found it impossible to pass even small sized suction catheters down the RETT. This was at first attributed to insufficient lubrication on the suction catheters and possibly to the acute angle taken by the RETT in the upper airway. Ventilation remained adequate (ETco$_2$ = 31–37 mm Hg; inspiratory pressure = 18–23 cm H$_2$O; SaO$_2$ = 100%; normal arterial blood gases). To facilitate suctioning it was decided to change the RETT to a polyvinylchloride endotracheal tube. Inspection of the RETT after removal revealed a flattened section 13.5–15.0 cm from the distal end (Figure 1). The diameter of the flattened lumen was about 2 mm at the narrowest point. There was a 0.5-cm longitudinal laceration through the silicone portion at a distance of about 14 cm from the distal tip; the wire reinforcement remained intact. This perforation lay just beside the imbedded cuff inflating (pilot) tube that runs the length of the RETT. The cuff in fact remained inflated during the time the obstructed RETT was in place.

Although there have been reports of structural problems with RETTs (1,2), patient-induced damage to these tubes has not been reported. Besides the inability to suction the trachea for secretions, if further obstruction of the tube had occurred, hypoventilation and hypoxemia would have been imminent. Further laceration of the tube and laceration of the cuff inflating tube obviously also would increase the likelihood of compromised ventilation and aspiration. If an oral placed silicone RETT is left in place postoperatively, it should be accompanied by a dependably positioned bite block.

Cliff O. Hoffmann, MD
Gene A. Swanson, MD
Department of Anesthesiology
Children's Hospital Medical Center of Akron
281 Locust Street
Akron, OH 44308

References

1. Cohen DD, Dillon JB. Hazards of armored endotracheal tubes. Anesth Analg 1972;51:856–8.

2. Ohn K, Wu W. Another complication of armored endotracheal tubes. Anesth Analg 1980;59:215–6.

FINALLY, AN EEG/EP MONITOR THAT'S RIGHT ON THE MONEY

WITH POWERFUL FEATURES:

- BAEP, BSEP, AEP, SEP, VEP
- Spectral analysis, CSA, raw EEG
- Continuous true EP/EEG monitoring
- On-line digital filtering, statistical analysis
- EEG coherence, power asymmetry
- Trend analysis with automatic alarms
- Hard disk storage, color display

FOR MONITORING:

- Carotid endarterectomy
- Cardiopulmonary bypass
- Orthopedic and neuro surgery
- Barbiturate coma
- Depth of anesthesia
- Hypothermia
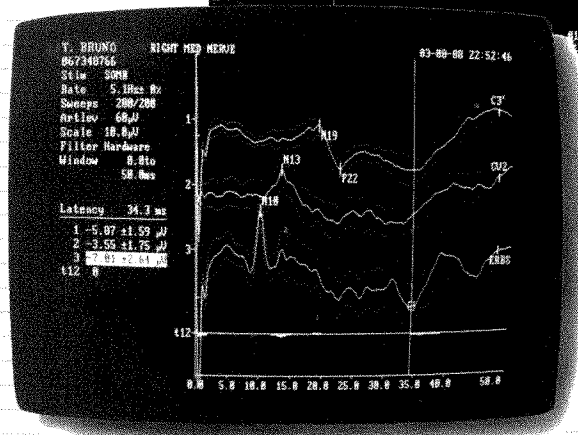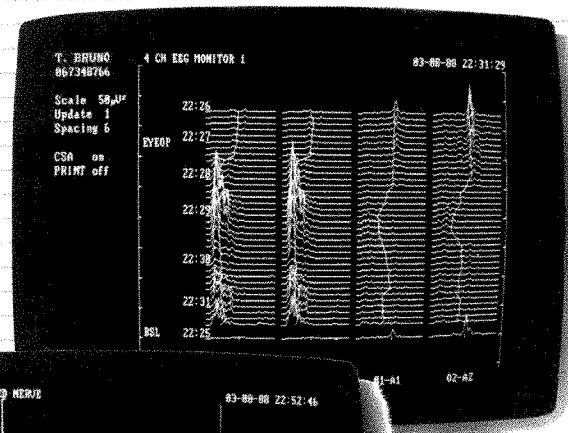
Everybody who has compared our new *Sentinel-4* EEG/EP Monitor to its leading competitors has been overwhelmingly impressed. It has a unique combination of capabilities including CSA, CEPA, statistics, trend analysis and automatic alarm, that make it easy to assess and evaluate neurologic function. Yet for all its sophistication, the *Sentinel-4* is extremely easy to use. Single stroke "soft keys", built-in help screens, pre-programmed test and monitoring protocols guide the operator from set up through printout. And most surprisingly of all . . . the price. It costs significantly less than any comparable system without compromising power, versatility or expandability.

For further information on the SENTINEL-4 call TOLL FREE 1-800-888-AXON